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(54) Oxadiazoles useful in the treatment of senile dementia.

(57) A class of novel oxadiazoles, substituted on one of the ring carbon atoms with a non-aromatic azacyclic or azabicyclic ring, and substituted on the other ring carbon atom with a substituent of low lipophilicity; are potent muscarinic agonists, and have good CNS penetrability. The compounds are therefore useful in the treatment of neurological and mental illnesses.

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OXADIAZOLES USEFUL IN THE TREATMENT OF SENILE DEMENTIA

The present invention relates to a class of oxadiazole compounds which stimulate central muscarinic acetylcholine receptors and therefore may
5 be useful in the treatment of neurological and mental illnesses whose clinical manifestations are due to involvement of specific populations of cholinergic neurones. Such diseases include presenile and senile
10 senile dementia (also known as Alzheimer's disease and Huntington's chorea, tardive dyskinesia, hyperkinesia, mania and Tourette Syndrome. The compounds of this invention are also useful analgesic agents and therefore useful in the treatment of
15 severe painful conditions such as rheumatism, arthritis, and terminal illness.

Alzheimer's disease, the most common dementing illness, is a slowly progressive neurological disorder characterised by marked
20 deficits in cognitive functions including memory, attention, language and visual perception capabilities. Although abnormalities in several central neurotransmitter systems have been documented (see P. Davies, Med. Res. Rev., 1983, 3, 221-236) in
25 Alzheimer's disease, the most consistent neurochemical deficiency involves presynaptic cholinergic markers in neocortex and hippocampus such as choline acetyl transferase activity, acetylcholinesterase activity and acetylcholine
30 synthesis (see P.J. Whitehouse et al., CRC Crit. Rev.Clin. Neurobiol., 1985, 1, 319-339). Muscarinic acetylcholine receptor sites located postsynaptically however are generally preserved in patients with

Alzheimer's disease.

Directly acting muscarinic agonists capable of stimulating such sites directly should therefore be beneficial in reversing the cholinergic deficiency in Alzheimer's disease and other diseases related to cholinergic dysfunction. However, most muscarinic agonists, including acetylcholine itself, are quaternary ammonium compounds incapable of penetrating the blood-brain barrier to any clinically significant extent following peripheral (e.g. oral) administration. Such agents fail to stimulate the desired central sites but instead induce undesired side-effects mediated exclusively peripherally-located muscarinic acetylcholine receptors.

The compounds of the present invention are potent muscarinic agonists but, being either secondary or tertiary amines with physiochemical properties (lipophilicity and pKa) consistent with CNS penetrability, can stimulate those central sites implicated in the neurodegenerative disorders discussed above.

The present invention provides an oxadiazole, substituted on one of the ring carbon atoms thereof with a non-aromatic azacyclic or azabicyclic ring system; and substituted on the other ring carbon with a substituent of low lipophilicity, or a salt thereof.

The novel compounds of this invention may be represented by structural formula (I):

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(I)

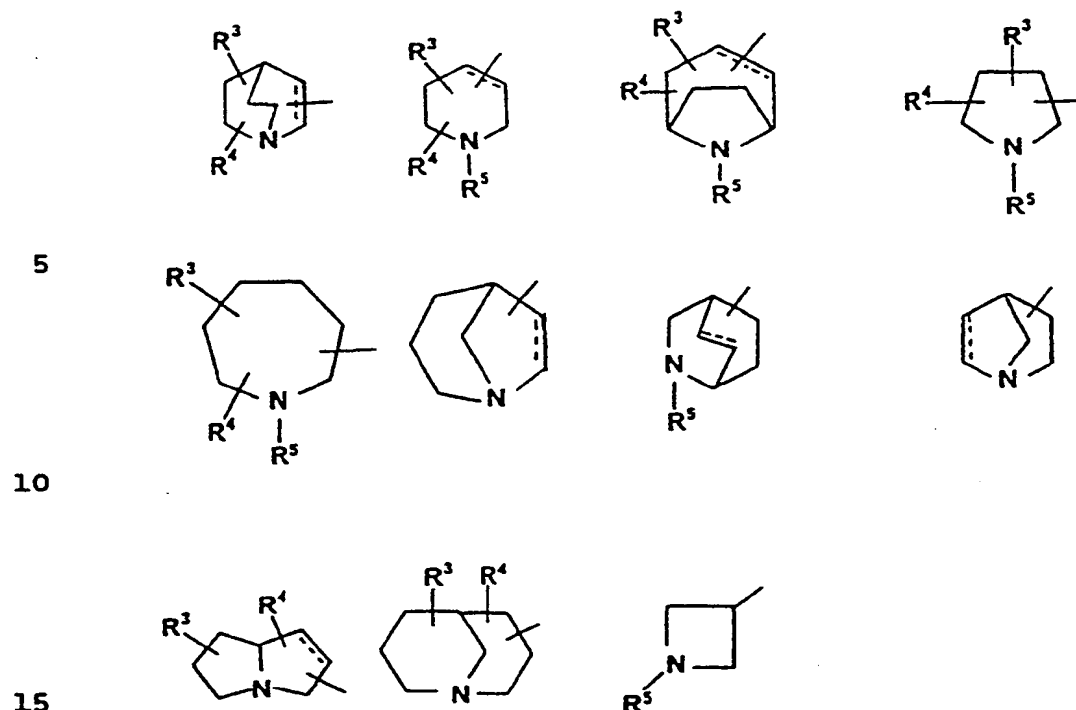
or a salt thereof; wherein one of X, Y, or Z is an oxygen atom and the other two are nitrogen atoms, and the dotted circle represents aromaticity (two double bonds) thus forming a 1,3,4-oxadiazole or 1,2,4-oxadiazole nucleus; R¹ represents a non-aromatic azacyclic or azabicyclic ring system; and R² represents a substituent of low lipophilicity.

Preferably the oxadiazole ring is a 1,2,4-oxadiazole.

The azacyclic or azabicyclic ring system is a non-aromatic ring system containing one nitrogen atom as the sole hetero atom. Suitably the ring system contains from 4 to 10 ring atoms, preferably from 5 to 8 ring atoms. The bicyclic systems may be fused, spiro, or bridged. Examples of suitable ring systems include the following:

- 4 -

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wherein the broken line represents an optional chemical bond;

the substituents R^3 and R^4 independently represent hydrogen, C_{1-4} alkyl, halo, C_{1-4} alkoxy, hydroxy or carboxy; or R^3 and R^4 together represent carbonyl;

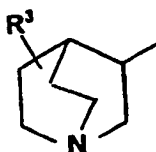
the group R^5 represents hydrogen or C_{1-4} alkyl. It will be appreciated that the nitrogen atom in the azacyclic or azabicyclic ring system will carry a lone pair of electrons.

Suitably the group R^3 is hydrogen or methyl; and R^4 is hydrogen, methyl or hydroxy. Preferably one or both of R^3 and R^4 is hydrogen.

Preferably the group R^5 represents hydrogen or methyl.

Suitably the azabicyclic ring system is a pyrrolidine, quinuclidine or 1-azabicyclo-[2,2,1]heptane ring. A preferred azabicyclic ring system is quinuclidine, of structure:

5



10

in particular where R^3 represents hydrogen, methyl or hydroxy.

The term "low lipophilicity" is intended to indicate that the group has a Rekker f value (hydrophobic fragment constant; see R. F. Rekker, "The Hydrophobic Fragmental Constant" Elsevier, 1977) of not greater than 1.5. For example the methyl group has a value of 0.7 and the ethyl group a value of 1.26. Indeed we have found that a propyl substituent provides a compound which is an antagonist rather than an agonist.

Thus the substituent of low lipophilicity, represented by the group R^2 in formula (I) may be, for example, hydrogen, halogen, $-\text{CF}_3$, $-\text{OR}^7$, $-\text{N}(\text{R}^7)_2$, $-\text{NHR}^7$, $-\text{NHNH}_2$, $-\text{CN}$, COR^8 , C_{2-5} alkenyl, C_{2-5} alkynyl, C_{1-2} alkyl, or C_{1-2} alkyl substituted with $-\text{OR}^7$, $-\text{N}(\text{R}^7)_2$, $-\text{SR}^7$, $-\text{CO}_2\text{R}^7$, $-\text{CON}(\text{R}^7)_2$ or halogen; wherein R^7 is hydrogen or C_{1-2} alkyl, and R^8 represents $-\text{OR}^7$, NH_2 , or NHR^7 .

Preferably the substituent of low lipophilicity is hydrogen, halogen, $-\text{CF}_3$, $-\text{OR}^7$, $-\text{NHR}^7$, $-\text{NHNH}_2$, $-\text{CN}$, $-\text{CO}_2\text{R}^8$, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-2} alkyl, or C_{1-2} alkyl

substituted with $-OR^7$, $-NHR^7$, $-SR^7$, $-CO_2R^7$, $-CON(R^7)_2$ or halogen. Particular values of the substituent, R^2 , are hydrogen, methyl, amino, methoxycarbonyl, and ethoxycarbonyl. A preferred group R^2 is amino.

- 5 One sub-class of compounds within the scope of the present invention is represented by formula (II):



- wherein R^1 and R^2 are as defined above; in particular wherein R^1 represents pyrrolidine, quinuclidine, tetrahydropyridine, piperidine, dehydrotropane, pyrrolizidine, azabicyclo-octane, any of which groups R^1 may be optionally substituted with C_{1-3} alkyl, or hydroxy; and R^2 represents C_{1-2} alkyl, amino, or C_{1-3} alkoxy carbonyl.

- 20 As used herein, the terms "alkyl" or "alkoxy" wherein the alkyl group is of 3 or more carbons, means straight chain alkyl, branched chain alkyl or cycloalkyl. The terms "alkenyl" and "alkynyl" include straight and branched chain. The term "halo" or "halogen" means fluoro, chloro or bromo--.

- 30 Most of the compounds of this invention have at least one asymmetric centre and often more than one; and can therefore exist as both enantiomers and diastereoisomers. In addition some exist as exo and endo isomers. It is to be understood that the invention covers all such isomers and mixtures thereof.

Also included within the scope of the present invention are salts of the novel compounds. It will be appreciated that salts of the compounds for use in medicine will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful if the preparation of the compounds of the invention or their non-toxic pharmaceutically acceptable salts. Acid addition salts, for example, may be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, and phosphoric acid. Where the novel compound carries a carboxylic acid group the invention also contemplates salts thereof, preferably non toxic pharmaceutically acceptable salts thereof, such as the sodium, potassium, and calcium salts thereof.

The method of treatment of this invention includes a method of treating Alzheimer's disease, senile dementia of the Alzheimer type, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania or Tourette syndrome by the administration to a patient in need of such treatment of an effective amount of one or more of the novel compounds.

This invention therefore also provides a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier.

It is advantageous, in order to reduce unwanted peripherally mediated side-effects, to incorporate into the composition a peripherally acting cholinergic antagonist (or anti-muscarinic

agent) Thus the compounds of the invention are preferably administered together with a peripheral cholinergic antagonist such as N-methylscopolamine; N-methylatropine propantheline, methantheline, or glycopyrrolate.

5 The compounds of the invention can be administered orally, parenterally, or rectally at a daily dose of about 0.01 to 10 mg/kg of body weight, preferably about 0.1 to 1 mg/kg and it may be administered on a regimen of 1-4 times a day. When a
10 cholinergic antagonist is administered, it is incorporated at its conventional dose.

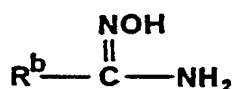
 The pharmaceutical formulation of this invention preferably are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile
15 parenteral solutions or suspensions, or suppositories for oral, parenteral or rectal administration. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g., conventional tableting
20 ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate, gums and other pharmaceutical diluents, e.g., water, to form a solid preformulation composition containing a homogenous mixture of a
25 compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogenous, it is meant that the active ingredient, is dispersed evenly throughout the composition so
30 that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills, and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to

about 500 mg. of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill
5 can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner
10 component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids or mixtures or polymeric acids with such materials as
15 shellac, shellac and cetyl alcohol, cellulose acetate, and the like.

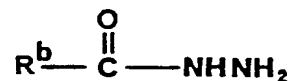
The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by
20 injection include aqueous solutions, suitably flavoured syrups, flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, peanut oil as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or
25 suspending agents for aqueous suspension include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone, and gelatin.

The compounds of this invention may be prepared by a process which comprises reacting a reactive derivative of a carboxylic acid of formula R^a-CO_2H , with either a compound of formula (IIIA) or (IIIB) or a salt thereof:

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(IIIA)

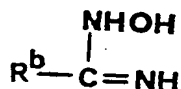
(IIIB)

wherein one of R^a and R^b is a non-aromatic
15 azacyclic or azabicyclic ring system, and the other is a group of low lipophilicity.

Suitable reactive derivatives of the acid R^a-CO_2H include esters, for example C_{1-4} alkyl esters, thio esters, for example pyridylthioester,
20 acid anhydrides, for example $(R^aCO)_2O$, acid halides, for example the acid chloride, orthoesters, and primary, secondary and tertiary amides.

When the compound of formula (IIIA) is employed the product of the reaction is a
25 1,2,4-oxadiazole. It will be appreciated that the compound (IIIA) can also be considered as the alternative tautomeric form:

30



A 3-substituted-1,2,4-oxadiazol-5-yl compound is produced if R^a represents the azacyclic or azabicyclic group and R^b in formula (IIIA) represents the substituent of low lipophilicity. In this case, a preferred reactive derivative of the acid R^aCO_2H is a C_{1-4} alkyl ester. The reaction is conveniently carried out in tetrahydrofuran, dimethylformamide or a lower alkanol such as ethanol, propanol or isopropanol at about 20° to $100^\circ C$ for about 1 to 6 hours.

10 A 5-substituted-1,2,4-oxadiazol-3-yl compound is produced by the process of this invention when R^a represents the substituent of low lipophilicity and R^b represents the azacyclic or azabicyclic group. For this reaction a suitable
15 reactive derivative is the acid chloride or the acid anhydride $(R^aCO)_2O$. The reaction may be carried out by treating compound (IIIA), in the cold, eg from about -5° to $+10^\circ C$, with the reactive derivative, followed by heating at about $80^\circ C$ - $120^\circ C$ for
20 about 1 to 6 hours.

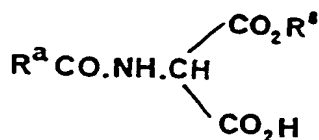
When the compound of formula (IIIB) is employed, the product of the process of this invention is a 1,3,4-oxadiazole. In this case, a preferred reactive derivative of the acid R^aCO_2H
25 is an orthoester of formula $R^aC(OR^8)_3$ where R^8 represents C_{1-3} alkyl. The process is conveniently effected by heating the hydrazide (IIIB) with the orthoester in a solvent such as methanol at reflux temperature for about 2 to 8 hours. An
30 intermediate of formula : $R^b.CO.NH.N=C(R^a)OR^8$, may be isolated by evaporation of the solvent. The intermediate is then treated with a strong base such as potassium t-butoxide or 1,8-diazabicyclo [5.4.0]

undec-7-ene, in butanol for about 10 to 24 hours at about 90 - 150°C.

After the above process is complete, one substituent of low lipophilicity can be converted to another. For example an amino group may be converted to chloro, or hydrazo, $-\text{NHNH}_2$, via the intermediacy of diazonium, $-\text{N}_2^+$. Similarly, a chloro substituent may be converted by reaction with a nucleophile such as methoxide; and alkoxy carbonyl groups may be converted, via carboxy, to an amino substituent $-\text{NH}_2$.

The compounds of this invention may also be prepared by:

- a) reacting a compound of formula (IV):
 $\text{R}^a-\text{CO}-\text{N}=\text{C}(\text{R}^b)\text{N}(\text{CH}_3)_2$, with hydroxylamine;
- b) oxidizing an oxadiazoline with an oxidizing agent such as potassium permanganate, nitrogen dioxide, or N-bromosuccinimide;
- c) when the substituent of low lipophilicity is amino, reacting a compound of formula (IIIA) with a cyanogen halide, such as cyanogen bromide.
- d) when the substituent of low lipophilicity is (C_{1-3}) alkoxy carbonyl, reacting a compound of formula:



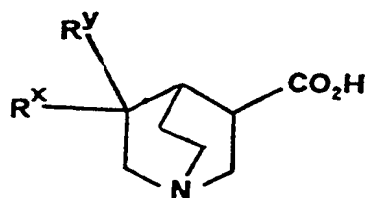
with nitrous acid;

e) when the desired product is a 1,3,4-oxadiazole, reacting a compound of formula $R^a.CO.NH.NH.CO.R^b$, with a dehydrating agent, such as $POCl_3$, at an elevated temperature.

5 The compound of formula (IV) above may be prepared by reacting an amide R^aCONH_2 , with a compound of formula $(CH_3O)_2C(R^b)N(CH_3)_2$.

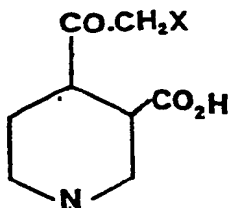
In any of the above reactions it may be necessary and/or desirable to protect any sensitive
10 groups in the compounds. For example, if R^a and/or R^b include amino, carboxy, hydroxy or thiol groups, these may be protected in conventional manner. Thus, suitable protecting groups for hydroxy groups include
15 silyl groups such as trimethylsilyl or dimethyl-t-butylsilyl, and etherifying groups such as tetrahydropyranyl; and for amino groups include benzyloxycarbonyl and t.butyloxycarbonyl. Carboxy
20 groups are preferably protected in a reduced form such as in the form of their corresponding protected alcohols, which may be subsequently oxidised to give the desired carboxy group. Thio groups may be
25 protected by disulphide formation, either with the thiol itself or with another thiol to form a mixed disulphide. The protecting groups may be removed at any convenient stage in the synthesis of the desired compound according to conventional techniques.

Certain intermediates employed in the above described processes are novel compounds. Accordingly this invention further provides an oxygenated quinuclidine of formula (V):



(V)

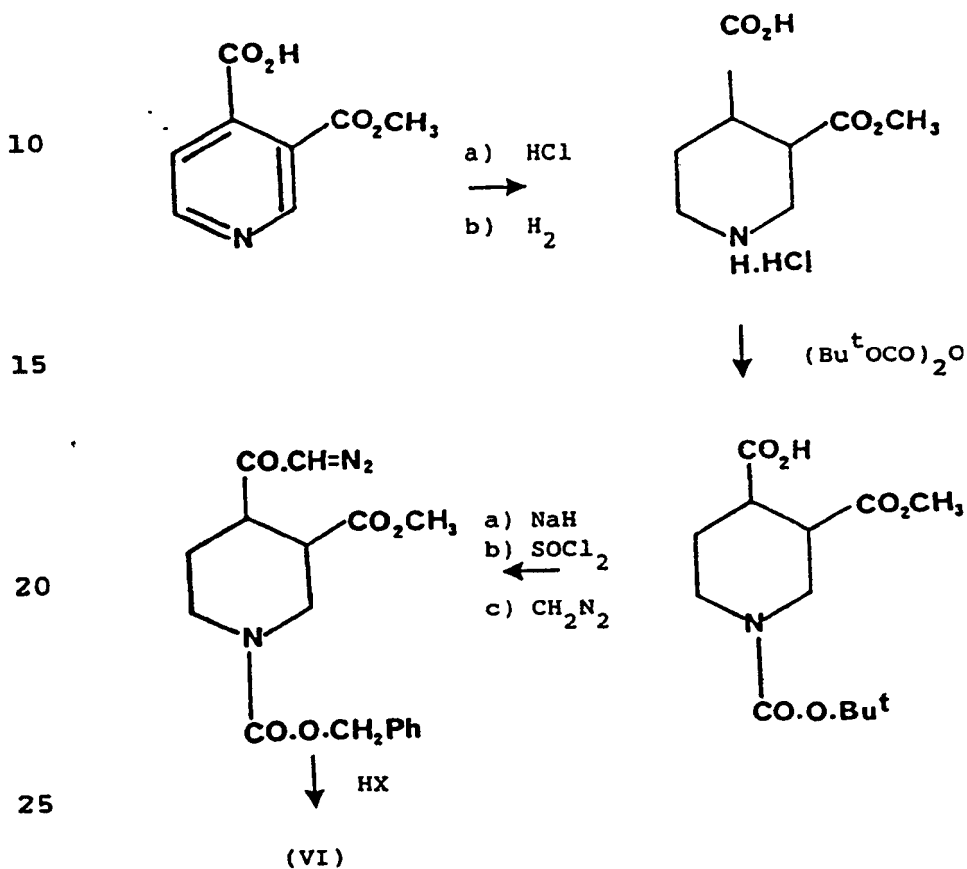
or a reactive derivative thereof wherein R^X represents H and R^Y represents hydroxy, or R^X and R^Y together represent oxygen. Compound (V) may be prepared by cyclisation of a compound of formula (VI):



(VI)

wherein X represents halogen.

The compound (VI) may be prepared by the
 5 following synthetic sequence:



The following Examples illustrate the
 30 preparation of compounds according to the invention.
 Each of the compounds of the Examples demonstrate an
 affinity for the muscarinic receptor, having an
 IC_{50} (concentration required to displace 50% of
 specific [3H]-N-methylscopolamine binding from rat
 cortical membrane preparations) significantly lower
 than 100 μ m. Agonist behaviour and

penetrability into the central nervous system of the compounds of the Examples were assessed in a rat behavioural model by measuring the ability of the compound to elicit a mouth movement response

- 5 characteristic of centrally-active muscarinic agonists (see Salamone et al, Psychopharm 1986 88,467). In this model, the compounds of all the Examples were active at doses of 10mg/kg or less.

In the Examples, all temperatures are in °C; THF
10 is tetrahydrofuran; and ether is diethyl ether.

EXAMPLE 1

- 15 1-Methyl-3-[5-(3-methyl-1,2,4-oxadiazol)-yl] pyrrolidine hydrochloride

(a) 1-Methyl-3-methoxycarbonyl-2-pyrrolidone

- To a solution of diisopropylamine (11.3 g,
20 0.11 mol) in THF (150 ml), at -78° was added n-butyl lithium (60 mls of a 1.6M solution in hexane). The solution was stirred for 0.5 hours before adding N-methyl-2- pyrrolidone (10.1 g, 0.1 mol) in THF (50 ml) over a period of 5 minutes. After 0.75 hours, a
25 solution of dimethylcarbonate (10.8 g; 0.12 mols) in THF (30 ml) was added and the reaction mixture allowed to warm to room temperature overnight. The reaction mixture was poured into water (50 ml) and extracted with dichloromethane (3 x 150 ml). The
30 combined extracts were dried (Na₂SO₄) and evaporated in vacuo. The crude product was chromatographed on silica gel using ethyl acetate/methanol (2:1) as eluant to afford the title

product as a clear liquid (4 g). δ (CDCl_3)
1.90-2.70 (2H, m, CH_2); 2.80 (3H, s, CH_3)
3.20-3.60 (3H, m, CH and CH_2); 3.70 (3H, s, CO_2
 CH_3).

5

(b) 1-Methyl-3-methoxycarbonyl-pyrrolidine

This was prepared from the foregoing pyrrolidone
by the procedure described by Rapoport (J. Org.
10 Chem., (1974). 39, 893).

(c) 1-Methyl-3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-
pyrrolidine hydrochloride

15 Activated molecular sieves (Type 4A, 1 g) were
vigorously stirred in absolute ethanol (25 ml) for
0.5 hours under nitrogen. Sodium metal (0.32 g, 13.9
m.mol) was added and allowed to dissolve before
adding acetamide oxime (1.00g, 13.6 mmol).
20 1-Methyl-3- carboxymethylpyrrolidine (0.5 g, 3.5
mmols) was added and the reaction mixture heated at
80° for 2 hours. The solution was then decanted from
the molecular sieves and the solvent removed in
vacuo. Dichloromethane (100 ml) was added to the
25 residue followed by water (20 ml) and the organic
products extracted into the dichloromethane layer.
The aqueous phase was extracted with dichloromethane
(3 x 50 ml), the combined extracts dried
(Na_2SO_4), evaporated, and the residue
30 chromatographed through alumina using
dichloromethane/methanol (97:3) as eluent, to afford
the title oxadiazole as a pale orange liquid (0.2 g).

The product was further purified as the hydrochloride salt, mp. 134°C (isopropyl alcohol ether); (found. C, 46.46; H, 6.75, N, 20.33%. $C_8H_{14}N_3OCl \cdot 0.25H_2O$ requires C, 46.15; H, 6.97, N, 20.19%; m/e 167 (M^+ of free base); δ (360MHz, D_2O) 2.41 (3H, s, CH_3); 2.48 (1H, m, CH); 2.72 (1H, m, CH); 3.05 (3H, s, CH_3) 3.62-4.20 (5H, m, CH and 2 x CH_2).

EXAMPLE 2

10

1-Methyl-3[5-(3-ethyl-1,2,4-oxadiazol)-yl]pyrrolidine hydrogen oxalate

This was prepared from 1-methyl-3-methoxy-
15 carbonylpyrrolidine and propionamide oxime as described in Example 1. The crude product was purified by chromatography through alumina using dichloromethane/methanol (19:1) as eluent to give the desired oxadiazole as a pale yellow liquid. The
20 product was further purified as the hydrogen oxalate salt mp. 109°, (isopropyl alcohol/ether); (Found: C, 48.86; H, 6.30, N, 15.79%. $C_{11}H_{17}N_3O_5$ requires C, 48.71; H, 6.27, N, 15.50%; m/e 181 (M^+ of free base); δ 1.22 (3H, t, $J = 7Hz$, CH_3 -
25 CH_2); 2.24 (1H, m, CH); 2.43 (1H, m, CH); 2.65 (2H, q, $J = 7Hz$, CH_2 CH_3); 2.75 (3H, s, CH_3); 3.21 (2H, m, CH_2-N); 3.40 (1H, m, $CH-N$); 3.59 (1H, m, $CH-N$); 3.95 (1H, m, $CH-OX$).

30

EXAMPLE 3

1, 3-Dimethyl-3[5-(3-methyl-1,2,4-oxadiazol)-yl]-pyrrolidine hydrochloride

(a) 1,3-Dimethyl-3-methoxycarbonyl-2-pyrrolidone

Sodium hydride (0.54 g of an 80% dispersion in oil, 16.5 mmol) was added to a solution of 3-methoxycarbonyl-1-methyl-2-pyrrolidone (2 g, 12 mmols) in THF (50 ml) and the suspension stirred for 0.5 hours. A solution of methyl iodide (3.60 g, 25 mmols) in THF (15 mls) was added and the reaction mixture stirred for 2 hours at room temperature. The solvent was removed in vacuo, and the organic product extracted from the sodium salts with dichloromethane (4 x 50 mls). The combined extracts were evaporated and the residue chromatographed through silica gel using 3% methanol in ethyl acetate as eluent, to afford the desired amine ester as a pale yellow liquid (1.63 g); δ (60MHz; CDCl_3) 1.45 (3H, s, CH_3); 1.55-2.80 (2H, m, CH_2); 2.88 (3H, s, CH_3); 3.10-3.60 (2H, m, CH_2); 3.70 (3H, s, CH_3).

(b) 1,3-Dimethyl-3-carbomethoxy pyrrolidine

A solution of 1,3-dimethyl-3-methoxycarbonyl-2-pyrrolidine (2.6 g, 15.7 mmol) in THF (50 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.79 g, 44.8 mmol) in THF (75 ml) at 0°. The reaction mixture was stirred at 20 for 16 hours and then heated under reflux for 5 hours. Excess reducing agent was destroyed with water and 15% sodium hydroxide and the resultant precipitate filtered. The filtrate was dried (MgSO_4) and evaporated to afford crude 1, 3-dimethyl-3-hydroxymethylpyrrolidine (1.68 g). This material in water (17.4 ml) and concentrated sulphuric acid (0.74 ml) was treated at 0° with a solution of chromium trioxide (1.09 g), concentrated sulphuric acid (0.74

ml) and water (17.4 ml). The reaction mixture was stirred at 0° for 5 minutes, heated at 100° for 5 minutes and cooled to 0° after which another charge of the chromium trioxide solution was added. Heating
5 at 100° for 0.5 hours was followed by cooling and then sodium metabisulphite was added to destroy excess oxidant. The pH was adjusted to 10 with 6N-sodium hydroxide, the mixture filtered and the filtrate acidified to pH2 with 6N-HCl. The water was
10 removed in vacuo, and a saturated solution of hydrogen chloride in methanol (200 ml) added to the dry residue. After 16 hours at 20°, the methanol was removed under vacuum, water (75 ml) was added and the pH adjusted to 8 with solid potassium carbonate. The
15 aqueous solution was extracted with dichloromethane (5 x 50 ml) and the combined extracts dried (Na₂SO₄) and evaporated. The residue was chromatographed through alumina using dichloromethane/methanol (49:1) as eluent, to afford
20 the ester as a pale orange liquid (0.82g); δ (60MHz, CDCl₃); 1.35 (3H, s, CH₃); 1.70 (1H, m, CH); 2.30 (3H, s, CH₃); 2.20-3.10 (2H, m, CH₂) and 3.65 (3H, s, CH₃).

25 (c) 1,3-Dimethyl-3[5-(3-methyl-1,2,4-oxadiazol)yl]-pyrrolidine hydrochloride

This was prepared from the foregoing ester using the method given in Example 1c. The crude product was chromatographed on alumina in ether to give the desired oxadiazole which was further purified by
30 addition of ethereal hydrogen chloride solution to give the hydrochloride salt (0.28 g), m.p. 178° (from isopropanol-ether); (Found: C, 49.59; H, 7.28; N, 19.07. C₉H₁₆N₃OCl requires C, 49.66; H, 7.36, N, 19.31%); m/e 181 (M⁺ of free base); δ (360

MHz, D₂O) 1.67 (3H, s, CH₃), 2.39 (3H, s, CH₃),
 2.40 (1H, m, CH); 2.70 (1H, m, CH); 3.03 (3H, s, CH₃);
 3.63 (3H, br m, CH₂ and CH) and 4.03 (1H, br s, CH).

5

EXAMPLE 4

3-Hydroxy-3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-
quinuclidine

This was prepared from methyl 3-hydroxy-
 10 quinuclidine-3- carboxylate (1.85 g, 10 mmol,
 prepared as described in Helv. Chim. Acta., (1954),
37, 1689) acetamide oxime (4.4 g, 50 mmol) and sodium
 (1.15 g, 50 mmol) in ethanol (40 ml) in the presence
 of activated molecular sieves (Type 3A, 10 g) as
 15 described in Example 1c. Recrystallization of the
 crude reaction product from ethyl acetate- petroleum
 ether (bp 60-80) afforded the desired oxadiazole
 product (185 mg) m.p. 139-140°; R_f = 0.9 on
 aluminium oxide in 1:9 methanol/dichloromethane;
 20 (Found: C, 55.0; H, 7.4; N, 19.1. C₁₀H₁₅N₃O₂
 requires C, 55.0; H, 7.3; N, 19.2%); m/e 209 (M⁺);
 δ (CDCl₃) 1.32-1.62 (3H, m, 5-CH₂ and 8-CH);
 2.12-2.22 (2H, m, 4-CH and 8-CH); 2.41 (3H, s,
 CH₃); 2.76-3.01 (5H, m, 2-CH, 6-CH₂ and 7-CH₂)
 25 and 3.71 (1H, A of AB system, J = 14Hz, 2-CH).

EXAMPLE 5

2-[5-(3-Methyl-1,2,4-oxadiazol)-yl]-quinuclidine
 30 hydrochloride

This was prepared from ethyl quinuclidine-2-
 carboxylate (1.83 g, 10 mmol) using the same
 quantities of reagents given in the previous Example

4. The crude free base so obtained was treated in ether with an excess of a saturated ethereal hydrogen chloride. Recrystallization of the resulting salt from isopropanol gave the title compound (0.70 g).
- 5 m.p. 224, R_f (of free base) = 0.6 in methanol-dichloromethane (1:9) on silica; (Found: C, 52.1; H, 6.9; N, 18.3. $C_{10}H_{16}ClN_3O$ requires C, 52.3; H, 7.0; N, 18.3%); m/e 193 (M^+ of free base); δ (D_2O) 1.74-2.0 and 2.03-2.09 (each 2M, each m,
- 10 5- CH_2 and 8- CH_2); 2.31-2.38 (2H, m, 3- CH_2); 2.46 (3H, s, CH_3); 2.51-2.54 (1H, m, 4-CH); 3.38-3.66 (4H, m, 6- CH_2 and 7- CH_2) and 5.11-5.17 (1H, m, 2-CH).

15

EXAMPLE 61-Methyl-3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-1,2,5,6-tetrahydropyridine hydrochloride

- Acetamide oxime (2.54g, 34 mmol) was added to
- 20 ethanol (25 ml) which had previously been stirred under dry nitrogen with molecular sieves (10 g, Type 4A) for 1 hour. Sodium (1.15 g, 0.05 mol) was added followed, after 0.5 hours, by methyl 1,2,5,6-tetrahydronicotinate hydrobromide (1 g, 4.2 mmol).
- 25 The mixture was heated under reflux for 2 hours, cooled, filtered and the filtrate evaporated. The residue in dichloromethane was washed with water and the oil obtained from the organic layer was purified by chromatography on silica in 1:9 methanol-
- 30 dichloromethane. Treatment of the resulting gum with ethereal hydrogen chloride gave the required oxadiazole hydrochloride (200 mg), m.p. 220-222°; (Found: C, 49.9; H, 6.4; N, 19.2. $C_9H_{13}N_3O \cdot HCl$ requires C, 50.1; H, 6.5; N, 19.5%); m/e 179 (M^+ of

free base); δ (CD_3OD) 1.57 (3H, s, CH_3);
 1.96-2.05 (2H, m, 5- CH_2); 2.26 (3H, s, NCH_3);
 2.70 (2H, broad t, $J = 6\text{Hz}$, 6- CH_2); 3.42 (2H, broad
 s, 2- CH_2) and 6.42-6.47 (1H, m, 4-CH).

5

EXAMPLE 7

1-Methyl-3-[5-(3-ethyl-1,2,4-oxadiazol)-yl]-1,2,5,6-tetrahydropyridine hydrochloride

- 10 This was prepared starting from methyl 1,2,5,6-tetrahydropyridine-3-carboxylate hydrobromide (1 g, 4.2 mmol), propionamide oxime (3.7 g, 42 mmol) and sodium (0.92 g, 40 mmol) as described in Example 6. The material was isolated as its hydrochloride salt (600 mg), m.p.
- 15 160-162°; (Found: C, 51.4; H, 7.2; N, 17.6. $\text{C}_{10}\text{H}_{15}\text{N}_3\text{O} \cdot \text{HCl} \cdot 0.25 \text{H}_2\text{O}$ requires C, 51.3; H, 7.1; N, 17.9%); m/e 192 ($\text{M}^+ - 1$ for free base); δ (D_2O) 1.31 (3H, t, $J = 7\text{Hz}$, CH_2CH_3); 2.81 (2H, q, $J = 7\text{Hz}$, CH_2CH_3); 2.83- 2.86 (2H, m, 5- CH_2);
- 20 3.11 (3H, s, NCH_3); 3.6 (2H, broad s, 6- CH_2); 4.20 (2H, broad s, 2- CH_2) and 7.34 (1H, m, 4-CH).

EXAMPLE 8

25 1-Methyl-3-[5-(3-methyl-1,2,4-oxadiazol)-yl]piperidine hydrochloride

- This was prepared as described in Example 6 but substituting ethyl 1-methylpiperidine-3-carboxylate (1.0 g) to give the title compound (700 mg); m.p.
- 30 245-246° (from isopropanol-ether); (Found: C, 49.6; H, 7.4; N, 19.4. $\text{C}_9\text{H}_{15}\text{N}_3\text{O} \cdot \text{HCl}$ requires C, 49.7; H, 7.4; N, 19.3%); m/e 181 ($\text{M}^+ - 1$ for free base); δ (CDCl_3) 1.57-1.70 (2H, m, CH_2); 2.02-2.06

(2H, m, CH₂); 2.38 (3H, s, CH₃); 2.43-2.58 and 2.60-3.01 (2H, each m, 6-CH₂); 2.89 (3H, broad s, NCH₃); 3.58-3.62 and 3.83-3.88 (each 1H, each broad d, J = 10Hz, 2-CH₂) and 4.02-4.11 (1H, m, 3-CH).

5

EXAMPLE 91-Methyl-4-[5-(3-methyl-1,2,4-oxadiazol)-yl]piperidine hydrochloride

10 This was prepared from ethyl
1-methyl-piperidine-4- carboxylate (1 g, 5.8 mmol),
acetamide oxime (1.68 g, 22.7 mmol) and sodium (0.7
g, 30 mmol) following the directions given in Example
6. After treatment of the intermediate free base with
15 ethereal hydrogen chloride purification of the salt
by recrystallization from isopropanol-ether gave the
desired oxadiazole hydrochloride (600 mg); m.p.
175-176°; (Found: C, 48.6; H, 7.5; N, 18.9.
C₉H₁₅N₃O.HCl.0.25H₂O requires C, 48.6; H,
20 7.5; N, 18.9%); m/e 181 (M⁺-1 for free base); δ
(CDCl₃) 2.07(2H, q, J = 11 Hz, 3- and 5- axial CH);
2.39 (3H, s, CH₃); 2.41-2.49 (2H, m, 3- and
5-equatorial CH); 2.94 (3H, s, NCH₃); 3.20 (2H,
overlapping dd, J = 11 Hz, 2- and 6- axial CH);
25 3.39-3.52 (1H, m, 4- CH) and 3.69 (2H, d, J = 11 Hz;
2-and 6-equatorial CH).

EXAMPLE 10

30 3-[3-(5-Methyl-1,2,4-oxadiazol)-yl]quinuclidine hydrochloride

(a) Quinuclidinone (24.2 g, 0.19 mol) and 2,4,6-triisopropylbenzene sulphonohydrazide (72 g, 0.24

mol) (250 ml) were stirred together in anhydrous methanol for 3 hours. Potassium cyanide (33.8 g, 0.51 mol) was added and the mixture heated under reflux for 5 hours. The material isolated, after
5 evaporation of the solvent, was partitioned between water and dichloromethane. The organic phase was dried (sodium sulphate) and evaporated and the residue fractionally distilled under reduced pressure to give 3-cyano-quinuclidine (6.1 g), approximate
10 b.p. 95-100° at 13 N.m⁻² (0.1 mmHg).

(b) A portion of the foregoing nitrile (1.36 g, 10 mmol) was treated in refluxing ethanol (40 ml) for 16 hours with hydroxylamine hydrochloride (2.08 g, 30 mmol) and potassium carbonate (2.8 g, 20 mmol). The
15 residue obtained after evaporation of the ethanol was dried over phosphorous pentoxide and then treated at 0° with acetic anhydride (40 ml). The mixture was heated under reflux for 3 hours, excess acetic anhydride removed and the residue partitioned between
20 dichloromethane and saturated potassium carbonate solution. The material isolated from the organic phase was purified by chromatography on neutral alumina (Grade III) in 1% methanol in dichloromethane. Treatment of the resulting oil with
25 ethereal hydrogen chloride followed by recrystallization of the salt from isopropanol-ether gave the required oxadiazole hydrochloride (610 mg); m.p. 191° (dec); (Found: C, 51.6; H, 6.9; N, 18.0. C₁₀H₁₅N₃O.HCl 0.25H₂O requires C, 51.3; H, 7.1; N, 17.9%); m/e 193 (M⁺ of free base);
30 δ (D₂O) 1.85-1.91 and 2.15-2.19 (each 2H, eaOh m, 5- and 8-CH₂); 2.54 (1H, dd, J = 4.5Hz, 4-CH); 2.63 (3H, s, CH₃); 3.3-3.47 (4H, m, 6- and 7-CH₂); 3.6-3.71 (1H, m, 3-CH) and 3.76-3.82 (2H, m, 2-CH₂).

EXAMPLE 113-[5-(3-Methyl-1,2,4-oxadiazol)-yl]quinuclidine
hydrochloride

5 Using the procedure outlined in Example 1c,
methyl 3- quinuclidine carboxylate (0.67 g, 3.9 mmol;
prepared as described by Grob in Helv. Chim. Acta.,
(1954), 37, 1689), acetamide oxime (1.78 g, 24.1
mmol) and sodium (0.09 g, 3.9 mmol) gave, after
10 heating under reflux in ethanol for 4 hours, the
required oxadiazole. Treatment of this material in
ether with hydrogen chloride in ether followed by
recrystallization of the resulting solid from
dichloromethane-ether, gave the hydrochloride salt
15 (0.43 g), m.p. 185-187°; (Found: C, 50.34; H, 7.00;
N, 17.66. $C_{10}N_{15}H_3O.H.HCl \cdot 0.5H_2O$ requires C,
50.31; H, 7.18; N, 17.60%); m/e 193 (M^+ of free
base); δ ($CDCl_3$) 1.81-1.93 and 2.07-2.27 (each
2H, each m, 5- CH_2 and 8- CH_2); 2.41 (3H, s,
20 CH_3); 2.58-2.62 (1H, m, 4-CH); 3.34-3.48 and 3.50-
3.61 (4H, each m, 6- CH_2 and 7- CH_2) and 3.69-3.76
and 3.86-3.92 (1H and 2H, each m, 2- CH_2 and 3-CH).

EXAMPLE 12

25

3-[5-(3-Methyl-1,2,4-oxadiazol)-yl]-2,3-
dehydroquinuclidine hydrochloride

This was prepared as described in Example 1c but
starting from methyl 2,3-dehydroquinuclidine-
30 3-carboxylate (0.5 g, 2.99 mmol), sodium (0.07 g,
7.99 mmol) and acetamide oxime (1.33 g, 17.96 mmol).
The product isolated after chromatography on alumina
eluting first with ethyl acetate and then 4% methanol

in ethyl acetate was recrystallized from dichloromethane-hexane to give 2-(1-aminoethylidenaminox)-3-[5-(3-methyl-1,2,4-oxadiazol)-yl]quinuclidine (0.15 g). This material (0.25 g, 5 0.94 mmol) in dichloromethane (30 ml) was treated for 15 minutes at 20 with potassium t-butoxide (1 g). After filtration, the material isolated from the filtrate was purified by alumina chromatography in methanol-dichloromethane (1:49). The solid obtained 10 after addition of ethereal hydrogen chloride was recrystallized from ether-dichloromethane to give the desired oxadiaxole (0.11 g); m.p. 167.5-169°; (Found: C, 52.59; H, 6.17; N, 18.45. $C_{10}H_{13}N_3O \cdot HCl$ requires C, 52.75; H, 6.2; N, 15 18.46); m/e 191 (M^+ for free base); δ (D_2O) 1.85-1.94 and 2.18-2.26 (each 2H, each m, 5- CH_2 and 8- CH_2); 2.46 (3H, s, CH_3); 3.23-3.32 and 3.70-3.78 (2H, and 3H, each m, 6- CH_2 , 7- CH_2 and 4-CH) and 7.69 (1H, d, $J = 1.4Hz$, 2-CH).

20

EXAMPLE 132-Methyl-3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-quinuclidine hydrochloride25 (a) 2-Methyl-3-methoxycarbonyl-2,3-dehydroquinuclidine

2-Methyl-3-oxoquinuclidine was prepared by the method of Nielsen (J. Org. Chem., (1966), 31, 1053) and converted to its hydrochloride salt by treatment 30 with ethereal hydrogen chloride.

The salt prepared above (17.5 g, 0.1 mol) was dissolved in water (17 ml) and cooled to 0°. Sodium cyanide (4.0 g, 0.1 mol) in water (15 ml) was added

dropwise and the reaction was stirred at 5 for 16 hours then filtered to give a white solid which was heated under reflux for 16 hours in concentrated hydrochloric acid (100 ml). The reaction was cooled
5 then concentrated in vacuo to give a solid which was treated (for 50 hours at room temperature) with methanol saturated with hydrogen chloride. The solution was concentrated in vacuo and the residue heated under reflux in thionyl chloride (55 ml) for
10 16 hours then cooled and concentrated under reduced pressure. The residue was dissolved in water which was made basic with potassium carbonate and extracted with dichloromethane. The organic phase was dried with sodium sulphate and concentrated to give an oil
15 which was chromatographed on neutral alumina (grade 3) eluting with dichloromethane, thus yielding 2-methyl-3-methoxycarbonyl-2,3- dehydroquinuclidine (2.6 g) which was characterised as its hydrogen chloride salt m.p. 198-199°; Rf = 0.33 in
20 dichloromethane on alumina; (Found C, 54.9; H, 7.3; N, 6.6; Cl, 16.8. $C_{10}H_{16}ClNO_2$ requires C, 55.2; H, 7.6, N, 6.4; Cl, 16.3%); m/e 181 (M^+ for free base); δ ($CDCl_3$) 1.73-1.84 and 1.98-2.08 (each 2H, each m, 5- CH_2 and 8- CH_2); 2.41 (3H, s, CH_3); 3.18-3.27 and 3.53-3.60 (each 2H, each m, 6- CH_2 and 7- CH_2), 3.49-3.53 (1H, m, 4-CH) and 3.84 (3H, s, OCH_3).
(b) The ester (650 mg, 3.6 mmol) prepared as described above was treated with hydrogen gas at 2.8×10^5 N.m⁻² (40 psi) over 10% Pd-C in ethanol
30 (40 ml) until uptake of gas ceased. The reaction mixture was filtered and concentrated in vacuo to give a colorless oil which was then added to a

- mixture containing molecular sieves (Type 4A) (10 g). sodium ethoxide solution from sodium (466 mg, 20 mmol) and ethanol (30 ml), and acetamide oxime (1.6 g, 21.6 mmol). The mixture was heated under reflux for 90 minutes then cooled, filtered and concentrated in vacuo. The residue was dissolved in water and extracted with ether which was dried with sodium sulphate. To this ether solution was added ethereal hydrogen chloride. The precipitated white solid was recrystallized from dichloromethane-ether yielding the quinuclidine oxadiazole (390 mg) hydrogen chloride salt m.p. 222°C; Rf 0.67 in CH_2Cl_2 containing 3% methanol on alumina; m/e 207 (M^+); (Found C, 54.3; H, 6.6; N 17.2; Cl, 15.4.
- $\text{C}_{11}\text{H}_{16}\text{ClN}_3\text{O}$ requires C, 54.6; H, 6.7; N, 17.4; Cl, 14.7%); δ (CDCl_3) 1.57 (3H, d, J = 6Hz, CHCH_3); 1.88-1.95 and 2.02-2.22 (each 2H, each m, 5- CH_2 and 8- CH_2); 2.40 (3H, s, CH_3), 2.60-2.66 (1H, m, 4-CH), 3.30-3.63 (5H, m, 3-CH, 6- CH_2 and 7- CH_2) and 4.01-4.10 (1H, m, 2-CH).

EXAMPLE 14

2-[5-(3-Methyl-1,2,4-oxadiazol)-yl]-2,3-dehyrotropane
 25 hydrochloride

- Methyl 3-oxopropane-2-carboxylate 19.7 g, 49 mmol; prepared as described in J. Org. Chem., (1957), 22, 1385 in methanol (150 ml) was treated at 0° with sodium borohydride (3.7 g, 98 mmol) added portionwise over 0.5 hours. After 1 hour at room temperature, water (400 ml) was added and the mixture extracted with dichloromethane. The material isolated from the combined organic extracts was purified by

chromatography on alumina (Grade III) in 3% methanol in dichloromethane to afford the hydroxyester (1.5 g), $R_f = 0.53$ on alumina in 1:9 methanol dichloromethane. A portion of this material (730 mg, 5 3.6 mmol) was treated at 5° with thionyl chloride (15 ml) and the solution heated under reflux for 2.25 hours. Excess thionyl chloride was removed and the residue in dichloromethane was treated with an excess of cold saturated potassium carbonate solution. The 10 organic layer was evaporated and the resulting oil was combined with the product from a similar preparation and used directly in the next step. Using the procedure given in Example 1c, the foregoing unsaturated ester (770 mg, 4.2 mmol), sodium (0.48 g, 15 21 mmol) and acetamide oxime (1.55 g, 21 mmol) gave the required oxadiazole after a reaction of time of 0.5 hours. Upon cooling, acetic acid (1.26 g, 21 mmol) was added before removing the molecular sieves by filtration. The filtrate was evaporated and the 20 residue partitioned between dichloromethane and water made basic by addition of solid potassium carbonate. The material isolated from the organic solvent was purified by chromatography on alumina in ethyl acetate and the resulting yellow oil in ether treated 25 with ethereal hydrogen chloride. Recrystallization of the salt from isopropanol gave the oxadiazole hydrochloride (135 mg), m.p. 201-202°; $R_f = 0.84$ on alumina in 10% methanol in dichloromethane; (Found: C, 54.3; H, 6.6; N, 17.0. $C_{11}H_{15}N_3O.HCl$ 30 requires C, 54.7; H, 6.7; N, 17.4%); m/e 205 (M^+ of free base); δ (D_2O) 2.05-2.11 and 2.39-2.72 (4-H, each m, 6-CH, and 7-CH₂); 2.43 (3H, s, CH₃); 2.94 (3H, s, NCH₃); 3.02-3.21 and 4.12-4.16 (each 1H,

each m, 4-CH₂): 4.70-4.86 (2H, m, 1-CH and 5-CH)
and 7.09-7.25 (1H, m, 3-CH).

EXAMPLE 15

5

3-[2-(5-Methyl-1,3,4-oxadiazol)-yl]quinuclidine
hydrogen oxalate

(a) Quinuclidine-3-carboxyhydrazide

Methyl quinuclidine-3-carboxylate hydrochloride
10 (10 g, 4.87 mmol) was partitioned between
dichloromethane and 2M-potassium carbonate solution.
The material isolated from the organic layer was
dissolved in methanol (10 ml) and hydrazine hydrate
(2 ml) and the solution heated under reflux for 22
15 hours. Evaporation of the solvents in vacuo yielded
the hydrazide (0.85 g) which was characterised as its
dihydrochloride salt, m.p. 227-230°; R_f = 0.3 on
alumina in methanol- dichloromethane (1:9); (Found:
C, 39.4; H, 7.2; N, 16.9; Cl, 28.4 C₈H₁₅N₃O.
20 2HCl.0.2H₂O requires C, 39.1; H, 7.1; N, 17.1; Cl,
28.8%); V_{max} (Nujol) 3300-2500, 2040, 1980 and 1700
cm⁻¹; m/e (free base) 169 (M⁺); δ (D₂O)
1.85-1.93 (2H, m, 5-CH₂); 2.00-2.09 (2H, m,
8-CH₂); 2.41- 2.46 (1H, m, 4-CH); 3.19-3.21 (1H, m,
25 3-CH); 3.30-3.37 (4-H, m, 6-CH₂, and 7-CH₂); 3.44
(1H, ddd, J = 13Hz, 13Hz and 2Hz, 2-CH anti to CO)
and 3.72 (1H, ddd, J = 13 Hz, 5.5Hz and 1.5Hz, 2-CH
syn to CO).

(b) 3-[2-(5-Methyl-1,3,4-oxadiazol)-yl]quinuclidine
30 hydrogen oxalate

A solution of the foregoing hydrazide (0.862 g,
5.1 mmol) in methanol (20 ml) and trimethyl

orthoacetate (6.5 ml, 51 mmol) was heated under reflux for 4 hours, cooled, and the solvent evaporated in vacuo. The residue was dissolved in 1-butanol (20 ml), potassium t-butoxide (0.86 g, 7.7 mmol) added and the solution heated under reflux for 17 hours. After removal of the solvent in vacuo, the residue was partitioned between dichloromethane and 2M potassium carbonate solution. The material isolated from the organic layer was purified by chromatography on grade 3 alumina in 1% methanol in dichloromethane to yield the desired oxadiazole (170 mg), which was characterised as its oxalate salt; m.p. 97-105°; R_f = 0.2 on alumina in 2% methanol in dichloromethane; (Found: C, 46.9; H, 5.6; N, 12.7. $C_{10}H_{15}N_3O \cdot 1.6(HO_2C)_2$ requires C, 47.0; H, 5.4; N, 12.5%); m/e 193 (M^+ of free base); δ (D_2O) 1.81-1.98 (2H, m, 8- CH_2); 2.11-2.18 (2H, m, 5- CH_2); 2.54 (3H, s, CH_3); 2.58-2.61 (1H, m, 4-CH); 3.31-3.45 (4H, m, 6- CH_2 , and 7- CH_2) and 3.75- 3.83 (3H, m, 2- CH_2 and 3-CH).

EXAMPLE 16

3-[5-(3-Amino-1,2,4-oxadiazol)-yl]quinuclidine
Sodium metal (1.56g, 0.068 mol) was added to a suspension of molecular sieve (type 4A, 12g) in absolute ethanol (60ml) stirred under nitrogen. After 15 minutes at room temperature, hydroxyguanidine hemisulphate hemihydrate (4.72g, 0.035 mol) was added and stirring continued a further 1 hour. Methyl quinuclidine-3-carboxylate (1g, 0.0059 mol) was added to the mixture which was then heated under reflux for 2 hours. After removal of the molecular sieve by filtration, the filtrate was evaporated in vacuo and

the resulting gum partitioned between dichloromethane and water. The material isolated from the organic layer was recrystallised from isopropanol-petroleum ether (b.p. 40-60) to afford the required

5 amino-oxadiazole (490mg), m.p. 158-160°; (Found: C, 55.5; H, 7.4; N, 28.5. $C_9H_{14}N_4O$ requires C, 55.7; H, 7.4; N, 28.9%); m/e 194 (M^+);

8 ($CDCl_3$) 1.36-1.48 (1H, m, 8-CH); 2.60-2.73 (3H, m, 8-CH and 5-CH₂); 2.17-2.23 (1H, m, 4-CH);

10 2.79-3.08 (5H, m, 6-CH₂, 7-CH₂ and 2-CH); 3.21-3.38 (2H, m, 3-CH and 2-CH) and 4.43 (2H, broad s, NH₂).

EXAMPLE 17A

15

endo-2-[5-(3-Amino-1,2,4-oxadiazol)-yl]
pyrrolizidine

(a) 2-Methoxycarbonyl-3H-pyrrolizine

20

This was prepared from pyrrole-2-aldehyde by the procedure described by Flitsch et al (Chem. Ber., (1968), 101, 3843).

(b) endo-2-Methoxycarbonylpyrrolizidine

This was prepared from 2-methoxycarbonyl-3H-pyrrolizine as described by Brandange et al, (Acta. Chem. Scand., (1973), 27, 433.

(c) endo-2-[5-(3-Amino-1,2,4-oxadiazol)-yl]
pyrrolizidine

30 Activated molecular sieves (Type 4A, 0.5g) were vigorously stirred in absolute ethanol (25ml) for 0.5 hr under nitrogen. Hydroxy guanidine sulphate (2.4g, 9.0mmol) was added and the reaction mixture stirred at room temperature for 1 hr. Sodium

metal (0.76g; 33mmol) was added and allowed to dissolve before adding a solution of endo-2-methoxycarbonylpyrrolizidine (0.56g; 3.3mmol) in ethanol (2ml). After heating the reaction at
5 reflux temperature for 2 hr, the solution was decanted from the molecular sieves and the solvent removed in vacuo. Dichloromethane (150ml) was added to the residue followed by water (15ml) and the material isolated from the organic layer was dried
10 (Na_2SO_4) and evaporated, and the residue chromatographed through alumina using dichloromethane/MeOH (95 : 5) as eluant to afford the title amino oxadiazole as a white crystalline solid (0.37g) mp. 133-135°C (isopropyl alcohol/petroleum
15 ether); (Found: C, 54.99; H, 7.22; N, 27.96 $\text{C}_9\text{H}_{14}\text{N}_4\text{O} \cdot 0.25 \text{H}_2\text{O}$ requires C, 54.40; H, 7.30; N, 28.21%; m/e 194 (M^+); δ (360MHz, CDCl_3) 1.20-2.10 (6H, m, 3x CH_2); 2.25-3.00 (2H, m, $\text{CH}_2\text{-N}$); 3.10 (1H, dd, $J = 11, 7.2\text{Hz}$, CH-N); 3.24
20 (1H, dd, $J = 11, 7.2\text{Hz}$, CH-N); 3.38-3.72 (2H, m, 2 x CH); and 4.32 (2H, br s, NH_2).

EXAMPLE 17B

25 exo-2-[5-(3-Amino-1,2,4-oxadiazol)-yl]pyrrolizidine

Activated molecular sieves (Type 4A, 0.5g) were vigorously stirred in absolute ethanol (25ml) for 0.5 hr under nitrogen. Hydroxy guanidine
30 sulphate (2.4g, 9.0mmol) was added and the reaction mixture stirred at room temperature for 1 hr. Sodium metal (0.76g; 33mmol) was added and allowed to

dissolve before adding a solution of
endo-2-methoxycarbonylpyrrolizidine (0.56g; 3.3mmol)
 in ethanol (3ml). After 48 hr at reflux temperature,
 the solution was decanted from the molecular sieves
 5 and the solvent removed in vacuo. Dichloromethane
 (150ml) was added to the residue followed by water
 (15ml) and the organic products isolated from the
 dichloromethane layer were chromatographed on alumina
 using dichloromethane/MeOH (95:5) as eluent to afford
 10 a 1 : 1 mixture of endo-and exo-oxadiazoles (0.15g).
 Further chromatography of the mixture through
 silica-gel using dichloromethane/MeOH (60 : 40) as
 eluent gave a fraction enriched 3 : 1 in the
exo-isomer, as a white crystalline solid, mp. 94-99°
 15 (isopropylalcohol/petroleum ether); (Found: C, 54.07;
 H, 7.23; N, 27.84 $C_9H_{14}N_4O \cdot 0.25H_2O$ requires
 C, 54.40; H, 7.30; N, 28.21); m/e 194 (M^+); δ
 (360MHz, $CDCl_3$) 1.50-2.10 (6H, m, 3 x CH_2);
 2.25-2.60 (2H, m, CH_2-N); 3.00-3.25 (2H, m,
 20 CH_2-N); 3.38-3.60 (2H, m, 2 x C-H); 4.32 (2H, br s.
 NH_2).

EXAMPLE 18

25 endo and exo-1-[5-(3-Amino-1,2,4-oxadiazol)-yl]
pyrrolizidines

(a) 1-Methoxycarbonylpyrrolizid-1-ene

This was prepared from 1-pyrroline-1-oxide
 and methyl γ -hydroxycrotonate as described by
 30 Tufariello et al. (J. Org. Chem., (1975), 40, 3866).

(b) endo-1-Methoxycarbonylpyrrolizidine

A solution of 1-methoxycarbonylpyrrolizid-1-
 ene (0.75g, 4.5mmol) in acetic acid (75mls) was

subjected to hydrogenation over rhodium on alumina (0.3g) in a parr shaker. After 1 hr the solvent was removed under vacuum, water (20ml) added and the solution made basic with potassium carbonate. The aqueous phase was extracted with chloroform (4 x 75mls), the combined extracts dried (Na_2SO_4) and evaporated to afford the title endo-ester (0.65g). The product was further purified as the hydrochloride salt, mp 129-131° (isopropylalcohol/ether); (Found: 10 C, 50.68; H, 7.83; N, 6.62. $\text{C}_9\text{H}_{15}\text{NO}_2 \cdot 0.5\text{H}_2\text{O}$ requires C, 50.35; H, 7.93; N, 6.53%); δ (60MHz; D_2O) 1.60-3.40 (11H, m, 5 x CH_2 and 1 x CH); 3.70 (3H, s, CO_2me) and 3.87-3.94 (1H, m, CH-N).

(c) endo and exo-1-[5-(3-Amino-1,2,4-oxadiazol)-
15 yl]pyrrolizidine

Activated molecular sieves (Type 4A, 0.5g) and hydroxy guanidine sulphate (1.26g, 4.73 mmol) were vigorously stirred in THF (60ml) for 0.25 hr, under nitrogen. Sodium hydride (0.56g of an 80% 20 dispersion in oil; 24mls) was added and the reaction mixture heated at 80°C for 0.5 hr before adding a solution of endo-1-methoxy-carbonyl-pyrrolizidine (0.8g, 4.73mmol) in THF (10ml). After heating at reflux temperature for 4 hr, the reaction mixture was 25 allowed to cool, poured into water (10ml) and extracted with dichloromethane (3 x 75ml). The combined extracts were dried (Na_2SO_4), evaporated, and the residue chromatographed on alumina using dichloromethane/MeOH (93.7) as eluent 30 to afford the title amino-oxadiazoles as a 1 : 1 mixture (0.25g). Further chromatography of the mixture through silica-gel using dichloromethane/MeOH (60 : 40) as eluent gave the endo and exo-

oxadiazoles as two separated components. The less polar product, assigned exo, was isolated as a white crystalline solid, mp 155-156° (isopropylalcohol):

(Found: C, 55.37; H, 7.32; N, 29.21 $C_9H_{14}N_4O$ requires C, 55.67; H, 7.22; N, 28.87%); δ (360MHz, $CDCl_3$) 1.63-2.40 (6H, m, 3 x CH_2); 2.58-2.78 (2H, m, CH_2-N); 3.05-3.12 (2H, m, CH_2-N); 3.30-3.40 (1H, m, CH -oxadiazole); 3.65-3.75 (1H, m, $CH-N$) and 4.20 (2H, br s, NH_2).

10

The more polar product, assigned endo was isolated as a white crystalline solid, mp. 137-140° (isopropylalcohol); (Found: C, 55.12; H, 7.38, N, 29.25 $C_9H_{14}N_4O$ requires C, 55.67; H, 7.22; N, 28.87%); δ (360MHz, $CDCl_3$) 1.20-1.25 (1H, m, 0.5 x CH_2); 1.70-1.77 (3H, m, 1.5 x CH_2); 2.11-2.38 (2H, m, CH_2) 2.50-2.60 (1H, m, 0.5 x CH_2-N); 2.85-2.95 (1H, m, 0.5x CH_2-N). 3.05-3.15 (2H, m, CH_2-N); 3.50-3.60 (1H, m, CH -oxadiazole); 3.81-3.89 (1H, m, $CH-N$) and 4.20 (2H, br s, NH_2).

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EXAMPLE 19

endo and exo-6-[5-(3-Amino-1,2,4-oxadiazol)-yl]-1-azabicyclo[3.2.1]octane

25

(a) 1-carboethoxymethyl-3-carboethoxypiperidine

Ethyl bromoacetate (21.2g, 127mmol) was added dropwise to a solution of 3-carboethoxypiperidine (40g, 254mmol) in ether 250ml, at 0°C. The reaction mixture was refluxed for 1 hr, the resultant precipitate filtered off and washed several

30

times with ether. The combined filtrates were evaporated to afford the title piperidine ester (27.6g); δ (60MHz, CDCl_3) 1.25 (3H, t, $J = 7\text{Hz}$, $\text{O}-\text{CH}_2-\text{CH}_3$); 1.27 (3H, t, $J = 7\text{Hz}$, $\text{O}-\text{CH}_2-\text{Me}$);
5 1.40-3.70 (9H, m, 4 x CH_2 and $\text{CH}-\text{CO}_2\text{Et}$); 3.20 (2H, s, $\text{CH}_2-\text{CO}_2\text{Et}$); 4.10 (2H, q, $J = 7\text{Hz}$, CH_2-Me) and 4.15 (2H, q, $J = 7\text{Hz}$, CH_2-Me).

(b) 1-Azabicyclo[3.2.1]octan-6-one

A mixture of ethanol (9ml) and toluene
10 (10ml) was added dropwise to a rapidly stirred suspension of potassium (6g) in toluene (30ml). at 120°C . After all the ethanol had been added the reaction mixture was stirred at 120°C for 1 hr before adding a solution of 1-carboethoxymethyl-3-
15 carboethoxy piperidine (15g, 61.7mmol) in toluene (40ml) dropwise at 140°C . The reaction mixture was heated for 3 hr at 140°C before adding concentrated hydrochloric acid (3 x 50ml), and refluxing the aqueous phase for 16 hr. The solvent was removed in
20 vacuo, water (100ml) added and the solution neutralised with potassium carbonate. The solution was extracted with dichloromethane (3 x 150ml, the combined extracts washed with saturated sodium chloride solution, dried (Na_2SO_4) and
25 evaporated. The crude product was chromatographed through silica-gel, eluting with dichloromethane/methanol (90 : 10) to give 1-azabicyclo[3:2:1]octan-6-one as a crystalline solid (1.1g); mp. $83-87^\circ$ (hexane); m/e 125 (M^+); δ (360 MHz, CDCl_3)
30 1.30-2.40 (5H, m, 2 x CH_2 , and CH); 3.12 (2H, s, CH_2-N); 2.60-3.60 (4H, m, 2 x CH_2-N).

(c) 6-(-1,3-Dithian-2-ylidene)-1-azabicyclo[3.2.1]octane

n-Butyl lithium (6.05ml of a 1.6M solution in hexane, 9.7mmol) was added dropwise to a solution of 2-trimethylsilyl-1,3-dithiane (1.86g, 9.7mmol), in THF (30ml) at -30°C and the reaction mixture stirred for 2 hr. A solution of 1-azabicyclo [3.2.1] octan-6-one (1.1g, 8.8mmol) in THF (10ml) was added dropwise and the reaction mixture allowed to warm to room temperature. Water (20ml) was added and extracted (3 x 50ml) with dichloromethane. The combined extracts were dried (MgSO₄) and evaporated and the residue chromatographed through alumina eluting with dichloromethane/methanol (97 : 3) to afford the title compound as a clear liquid, (2g), m/e 227 (M⁺); δ (60MHz; CDCl₃) 1.10-2.90 (15H, m, 7 x CH₂ and CH); 3.38 (2H, AB q, J = 17Hz, CH₂-C=C).

(d) 6-Carbomethoxy-1-azabicyclo[3.2.1]octane

The preceding dithiovinylidene (2g; 8.8mmol) was dissolved in methanol, saturated with hydrogenchloride, (75ml) and stirred at 55°C for 5 hr. The solvent was removed in vacuo, the residue taken up into water (7ml), basified to pH 10 with potassium carbonate and extracted into dichloromethane (4 x 50mls). The combined extracts were dried (Na₂SO₄), evaporated, and the residue chromatographed through alumina using dichloromethane/methanol (96.4) as eluant to afford the desired ester as a clear liquid (0.5g). The hydrochloride salt was prepared, mp 151-154° (isopropyl alcohol): (Found: C, 51.92; H, 7.65; N, 6.83. C₉H₁₆NO₂Cl 0.125H₂O requires C, 51.98, H, 7.82; N, 6.73%); δ (360MHz; D₂O) 1.30-1.41

(1H, m, 0.5 x CH₂); 1.54-1.72 (3H, m, 1.5 x CH₂);
 2.41-2.48 (1H, m, CH-C-CO₂Me); 2.78-2.87 (5H, m,
 CH-CO₂Me and 2 x CH₂-N); 3.05-3.20 (2H, m,
 CH₂-C-CO₂Me) and 3.68 (3H, s, CO₂Me).

5

(e) endo and exo-6-[5-(3-Amino
1,2,4-oxadiazol)-yl]-1-azabicyclo[3.2.1] octane

These were prepared from 6-carbomethoxy-
 10 1-azabicyclo[3.2.1]octane and hydroxyguianidine
 sulphate as described in Example 1, heating the
 sodium ethoxide reaction mixture for 16hr. The crude
 product was purified by chromatography through
 alumina using dichloromethane/methanol (19:1) as
 15 eluant to give a white crystalline solid.
 Recrystallisation of the product from isopropyl
 alcohol/hexane gave 6-[5-(3-amino-1,2,4-oxadiazol)-
 yl-1-azabicyclo[3.2.1]octane (isomer A) as a white
 crystalline solid, mp 156-158°; (Found: C, 53.17; H,
 20 7.37; N, 27.57. C₉H₁₄N₄O.0.5H₂O requires C,
 53.20; H, 7.39; N, 27.59) δ (360MHz, CDCl₃)
 1.40-1.96 (4H, m, 2 x CH₂); 2.55 (1H, br s, CH);
 2.70-3.00 (4H, m, 2 x CH₂); 3.10-3.40 (3H, m, CH₂
 and CH); 4.40 (2H, br s, NH₂); m/e 194 (M⁺).
 25 Repeated recrystallisation of the product
 obtained from the filtrate of the initial
 recrystallisation gave a pure sample of 6-[5-
 (3-amino-1,2,4-oxadiazol)-yl]-1-azabicyclo
 [3.2.1]octane, (isomer B) mp 190-195° (isopropyl
 30 alcohol); (Found: C, 53.11; H, 7.36; N, 27.53.
 C₉H₁₄N₄O. 0.5H₂O requires C, 53.20; H, 7.39;
 N, 27.59%]; δ (360MHz, CDCl₃) 1.20-1.80 (4H, m, 2
 x CH₂); 2.60 (1H, br s, CH); 2.80-3.00 (5H, m, 2 x

CH_2 and CH -oxadiazole); 3.43 (2H, br s, $\text{CH}_2\text{-N}$);
4.34 (2H, br s, NH_2).

EXAMPLE 20

5

3-[5-(3-Amino-1,2,4-oxadiazol)-yl]pyrrolidine hydrochloride

(a) 1-Benzyl-3-hydroxymethylpyrrolidine

This was prepared from itaconic acid and
10 benzylamine by the procedure described by Feldkamp et
al. J. Am. Chem. Soc., (1961), 1519.

(b) 1-Benzyl-3-carboethoxypyrrolidine

1-Benzyl-3-hydroxymethylpyrrolidine was
oxidised to 1-benzyl-3-carboethoxypyrrolidine by a
15 procedure described by Rapoport (J. Org. Chem.,
(1974), 39, 893) for the oxidation of 1-methyl-3-
hydroxymethylpyrrolidine to the corresponding methyl
ester. The crude product did not require further
purification. δ (60MHz, CDCl_3) 1.20 (3H, t, J =
20 6.5 Hz, Me); 1.90-3.20 (7H, m, 3x CH_2 and
 $\text{CH-CO}_2\text{Et}$); 3.60 (2H, s, $\text{CH}_2\text{-N}$); 4.10 (2H, q, J =
6Hz, Me- CH_2) and 7.25 (5H, m, C_6H_5).

(c) 3-Carboethoxypyrrolidine

A solution of 1-benzyl-3-carboethoxy-
25 pyrrolidine (2g, 8.6mmol) in ethanol (75ml) was
subjected to hydrogenolysis over $\text{Pd}(\text{OH})_2$ on a parr
shaker for 48 hr. The catalyst was filtered off, the
solvent removed under vacuum, and the residue
chromatographed through alumina using dichloromethane/
30 methanol (85:15) as eluant, to give the title product
as a clear liquid (0.6g); δ (60MHz, CDCl_3) 1.20
(3H, t, J = 7Hz, OCH_2CH_3); 1.70-2.30 (2H, m,
 CH_2); 2.50-3.20 (5H, m, 2 x $\text{CH}_2\text{-N}$, and CH-CO_2
Et); 4.10 (2H, q, J = 7Hz, OCH_2CH_3).

(d) 3-[5-(3-Amino-1,2,4-oxadiazol)-yl]pyrrolidine hydrochloride

This was prepared from 3-carboethoxy-
5 pyrrolidine and hydroxy guanidine sulphate by the
procedure described in Example 1. The crude product
was chromatographed through alumina using
dichloromethane/MeOH (10 : 1) as eluant, to afford
the title amino-oxadiazole as a clear oil. Addition
10 of ethereal hydrogen chloride to a solution of the
product in ether/MeOH (3 : 1) gave the hydrochloride
salt; mp 168-172° (isopropylalcohol). (Found: C,
36.80; H, 5.60; N, 27.90; Cl, 17.69. $C_6H_{11}N_4O$
Cl. $0.4H_2O$ requires C, 36.42; H, 5.96; N, 28.32;
15 Cl, 17.95%); δ (360MHz, D_2O) 2.00-2.50 (2H, m,
 CH_2); 2.80-3.60 (5H, m, 2 x CH_2 and CH).

EXAMPLE 21A

20 endo-6[5-(3-Methyl-1,2,4-oxadiazol)yl]-2-azabicyclo
[2.2.2]octane

(a) endo and exo-2-Benzylloxycarbonyl-6-
methoxycarbonyl-2-azabicyclo[2.2.2]oct-7-ene

25

Sodium borohydride (5.7g, 0.15mmol) was
added portionwise to a solution of anhydrous pyridine
(12.1ml, 0.15mmol) in methanol (100ml), at -65°C.
The mixture was cooled to -70°C and
30 benzylchloroformate (24.8ml, 0.15mmol) added
dropwise, and stirred for 1 hr. The mixture was
warmed slowly to room temperature, the solvent
removed in vacuo and the residue taken up into water

- (40ml) and extracted into ether (2 x 50ml). The ethereal extracts were washed with 0.1N hydrochloric acid (10ml) and water (3 x 10ml), dried (MgSO_4) and evaporated. The residue was dissolved in
- 5 acetonitrile (90ml) and methyl acrylate (13.25g, 0.154mmol) and hydroquinone (1.0g) added. The reaction mixture was heated at reflux for 6.5 days, the solvent removed under vacuum and the residue chromatographed through silica gel, eluting with
- 10 toluene/ethyl acetate (10 : 1) to give a mixture of endo and exo products. The mixture was subjected to chromatography through alumina using dichloromethane as eluant to give the endo-Diels Alder product (6.03g) and exo-adduct (1.72g) as separated
- 15 components. δ endo-(360 MHz, CDCl_3) 1.80-1.90 (2H, m, CH_2); 2.81-3.38 (4H, m, CH_2 and 2 x CH); 3.65 (3H, s, OMe); 5.05-5.20 (3H, m, CH_2 -N, and CH); 6.25-6.35 (1H, m, vinyl H); 6.35-6.48 (1H, m, vinyl H); 7.30-7.42 (5H, m, C_6H_5). δ exo
- 20 (360MHz, CDCl_3); 1.50-1.60 (1H, m, CH); 2.05-2.15 (1H, m, CH); 2.52-2.58 (1H, m, CH); 2.75-2.80 (1H, m, CH); 3.00-3.12 (1H, m, CH); 3.36-3.48 (1H, m, CH); 3.65 (3H, s, CO_2Me); 4.93-5.10 (3H, m, CH_2 -N and CH) and 7.25-7.38 (5H, m, C_6H_5).
- 25 (b) endo-6-Carbomethoxy-2-azabicyclo[2.2.2]octane
 A solution of endo-2-benzyloxycarbonyl-6-carbomethoxy-2-azabicyclo[2.2.2]oct-7-ene (3.56g, 11.8mmol) in methanol (35ml) was subjected to hydrogenation over Pd/C (0.35g), at atmospheric
- 30 pressure for 2 hr. The catalyst was filtered and the solvent removed in vacuo to afford the title ester as a clear oil (1.98g). The oxalate salt was prepared; mp 109-110° (dichloromethane); (Found: C, 48.53, H, 5.97, N, 4.62. $\text{C}_9\text{H}_{15}\text{NO}_2$ 1.3 $\text{H}_2\text{C}_2\text{O}_4$

requires C, 48.66, H, 6.19; N, 4.89%); δ (360MHz, D₂O) 1.71-2.10 (7H, m, 3 x CH₂ and CH); 3.15-3.28 (3H, m, CH₂-N, and CH-CO₂Me); 3.75 (3H, s, CO₂Me) and 3.81 (1H, br s, CH-N).

5 (c) endo-6[5-(3-Methyl-1,2,4-oxadiazol)yl]-2-azabicyclo[2.2.2]octane

This was prepared from acetamideoxime and endo-6-carbomethoxy-2-azabicyclo[2.2.2]octane by the procedure described for Example 18. The crude
10 product was chromatographed through alumina using dichloromethane/methanol (19 : 1) as eluant to give the title endo-methyloxadiazole as a clear liquid. The hydrochloride salt was prepared, mp 215-216° (isopropylalcohol/ether); (Found: C, 51.81, H, 6.87; N, 18.32. C₁₀H₁₅N₃O.HCl requires C, 52.28; H, 7.02; N, 18.29%); δ (360MHz, D₂O) 1.80-2.05 (4H, m, 2 x CH₂); 2.10-2.30 (2H, m, CH₂); 2.25-2.40 (1H, m, CH); 2.40 (3H, s, Me); 3.34 (2H, s, CH₂-N); 3.82-3.92 (1H, m, CH-oxadiazole) and 3.80-3.95 (1H, 20 m, CH-N).

EXAMPLE 21B

25 exo-6[5-(3-Methyl-1,2,4-oxadiazol)yl]-2-azabicyclo[2.2.2]octane

(a) exo-6-carbomethoxy-2-azabicyclo[2.2.2]octane

A solution of exo-2-benzyloxycarbonyl-6-carbomethoxy-2-azabicyclo[2.2.2]oct-7-ene (1.02g, 3.4mmol) in methanol (20ml) was hydrogenated over
30 Pd/C (0.1g) at atmospheric pressure, for 12 hr. The catalyst was filtered and the solvent removed under vacuum to give the title saturated ester as a yellow liquid (0.29g). The hydrochloride salt was prepared.

mp 157-158° (isopropylalcohol/ether); (Found: C, 52.43, H, 7.73; N, 6.34. $C_9H_{15}NO_2$ HCl requires C, 52.55, H, 7.84; N, 6.80); δ (360MHz, D_2O) 1.60-1.85 (4H, m, 2 x CH_2); 1.99-3.06 (4H, m, 2 x CH and CH_2); 3.24 (2H, br s, \underline{CH}_2-N); 3.78 (3H, s, CO_2 Me) and 3.75-3.90 (1H, m, $\underline{CH}-N$).

(b) exo-6-[5-(3-Methyl-1,2,4-oxadiazol)-yl]-2-azabicyclo[2.2.2]octane

This was prepared from acetamideoxime and
 10 exo-6-carbomethoxy-2-azabicyclo[2.2.2]octane by the procedure described for Example 18. The crude product was purified by chromatography through alumina using dichloromethane/methanol (10 : 1) as eluant to give the desired exo-methyl oxadiazole as a
 15 yellow liquid. The hydrochloride salt was prepared, mp 183-185° (isopropyl alcohol/ether); (Found: C, 52.23; H, 6.96; N, 18.20. $C_{11}H_{15}N_3O.HCl$ requires C, 52.28; H, 7.02; N, 18.29%) δ (360MHz, D_2O) 1.70-2.10 (2H, m, \underline{CH}_2); 2.10-2.40 (4H, m, 2 x
 20 CH_2); 2.45 (3H, s, Me); 2.32-2.50 (1H, m, \underline{CH}); 3.29 (2H, br s, \underline{CH}_2-N); 3.60-3.79 (1H, m, $\underline{CH}-oxadiazole$) and 3.93-4.10 (1H, m, $\underline{CH}-N$).

EXAMPLE 22

25

3-[5-(3-Ethoxycarbonyl-1,2,4-oxadiazol)-yl]quinuclidine Hydrochloride

Methyl 3-quinuclidinyl carboxylate
 30 hydrochloride (9.3g, 45.2mmol) was heated under reflux in concentrated hydrochloric acid (100ml) for 16 hours. The reaction was concentrated under reduced pressure and the residue heated under reflux

in thionyl chloride (150ml) for 2.5 hours. The solution was concentrated in vacuo and the remaining solid suspended in dry tetrahydrofuran (150ml) under a nitrogen atmosphere. Ethoxy-carbonyl formamide oxime (7.8g, 59.0mmol), prepared by the method of Warburton et al (J. Chem. Soc. (C), 1522, (1966)), in tetrahydrofuran (150ml) was added dropwise and the reaction was stirred for 16 hours. The solution was evaporated under reduced pressure and the residue dissolved in water which was made basic with K_2CO_3 . The solution was extracted with CH_2Cl_2 (3 x) and the combined extracts dried ($MgSO_4$) and evaporated in vacuo. The residue was dissolved in dry dioxan (200ml) and heated under reflux over type 4A molecular sieves (70g) for 24 hours. The reaction was filtered and concentrated under reduced pressure to give a residue which was treated with ethereal HCl to give, after recrystallisation from propan-2-ol, the title compound; mp 170-171°C; (Found: C, 49.90; H, 6.31; N, 14.61. $C_{12}H_{17}N_3O_3$. HCl requires C, 50.09; H, 6.31; N, 14.61%) ν_{max} (nujol) $1748cm^{-1}$ (C=O); m/e 251 (M^+ of free base); δ (360MHz, D_2O) 1.42 (3H, t, J = 7.2Hz, CH_3), 1.80-2.01 and 2.10-2.28 (each 2H, each m, $5CH_2$ and $8CH_2$), 2.68-2.73 (1H, m, 4CH), 3.34-3.52 (4H, m, $6CH_2$ and $7CH_2$), 3.88 (2H, d, J = 8.2Hz, $2CH_2$), 4.00-4.08 (1H, m, 3CH) and 4.52 (2H, q, J = 7.2Hz, OCH_2).

30

EXAMPLE 231-Methyl-3-[5-(3-amino-1,2,4-oxadiazol)-yl]pyrrolidine

This was prepared from 1-methyl-3-methoxy carbonylpyrrolidine (336mg, 2.35 mmol), hydroxy-

EXAMPLE 231-Methyl-3-[5-(3-amino-1,2,4-oxadiazol)-yl]pyrrolidine

This was prepared from 1-methyl-3-methoxy
5 carbonylpyrrolidine (336mg, 2.35 mmol), hydroxy-
guanidine sulphate (1.88g, 14.1 mmol), and sodium
(621 mg, 25.8 mmol) in absolute ethanol (50 ml)
exactly as described in example 1. The crude product
was purified by chromatography on alumina in 5%
10 methanol in dichloromethane and then recrystallised
from isopropanol-petroleum ether to afford the
desired aminooxadiazole (140 mg) mp 62-65°; (found:
C, 50.52; H, 7.27; N, 33.25. $C_7H_{12}N_4O$ requires
C, 50.00; H, 7.14; N, 33.33%); m/e 168 (M^+); δ
15 (360 MHz, $CDCl_3$) 2.14-2.23 and 2.27-2.35 (each 1H,
each m, 2 x CH); 2.39 (3H, s, NCH_3); 2.58-2.65 (2H,
m, NCH_2); 2.76-2.81 and 2.90-2.95 (each 1H, each m,
2 x NCH); 3.46-3.55 (1H, m, 3-CH) and 4.37 (2H,
broad, s, NH_2).

20

EXAMPLE 243-[5-(3-Amino-1,2,4-oxadiazol)-yl]-1-azabicyclo-
[2,2,1]heptane

25

a) 1-Benzyl-3-ethoxycarbonylpyrrolidine

A solution of 1-benzyl-3-hydroxymethylpyrrolidine
(60g, 0.314 mol; J. Org. Chem., (1961), 26, 1519) in
conc. sulphuric acid (7.3ml) and water (350ml) was
30 treated at 0° with a solution of chromium trioxide
(26.2g) in conc. sulphuric acid (18ml) and water
(410ml). The mixture was stirred at 0° for 5 min.

100° for 2 min and then cooled back to 0°. A further charge of the chromium trioxide solution was then added and the mixture heated at 100° for 0.5h. After cooling again to 10°, excess sodium metabisulphite was added to destroy any remaining oxidant and the pH adjusted to 10 with 6N-sodium hydroxide solution. After filtration, the mixture was acidified to pH 2 with 6N-hydrochloric acid and the solution evaporated. The rigorously dried residue was treated at 20° for 16h with anhydrous ethanol saturated with hydrogen chloride. The gum after evaporation of the solvent was partitioned between dichloromethane and water made basic with excess potassium carbonate and the required ethyl ester isolated from the organic layer (25g): δ (60 MHz, CDCl_3) 1.20 (3H, t, J = 6.5 Hz, CH_3); 1.9-2.2 (5H, m, 2 x CH_2 and CH); 3.60 (2H, s, CH_2 Ph); 4.10 (2H, q, J = 6.5 Hz, CH_2 CH_3) and 7.23 (5H, broad 2, C_6H_5).

b) 1-Ethoxycarbonylmethyl-3-ethoxycarbonyl-pyrrolidine

The foregoing 1-benzylpyrrolidine (18g) in ethanol (400ml) was subjected to hydrogenolysis over $\text{Pd}(\text{OH})_2$ (5g) at 50 psi in a Paar shaker for 72h. After filtration, the solvent was evaporated and the resulting oil purified by chromatography on alumina in methanol-dichloro-methane (1:19) to give 3-ethoxycarbonyl-pyrrolidine (8g) as a colourless oil. This amine (7.75g, 54mmol) in ether (70ml) was treated at 0° with a solution of ethyl bromoacetate (4.53g, 27mmol) in ether (40ml) in the presence of solid potassium carbonate (5g). After 0.5h at 0° and 1h at reflux, the precipitated solid was removed by filtration and the residue isolated from the

filtrate purified by chromatography on alumina in dichloromethane to give the diester (5.56g); δ (60MHz, CDCl_3) 1.25 (6H, t, $J = 7\text{Hz}$, $2 \times \text{CH}_3$); 2.1-3.2 (7H, m, $3 \times \text{CH}_2$ and CHCO); 3.3 (2H, s, CH_2CO) and 4.15 and 4.20 (each 2H, each q, each $J = 7\text{Hz}$, $2 \times \text{OCH}_2$).

c) 1-Azabicyclo[2,2,1]heptan-3-one

A mixture of ethanol (4.5ml) and toluene (6ml) was added dropwise to a rapidly stirred suspension of potassium (2.66g, 68.2mmol) in toluene (15ml) at 120° under nitrogen. After 1h at this temperature, a solution of the foregoing diester (6.24g, 27.3mmol) in toluene (25ml) was then added and the mixture heated at 140° for 3h. Concentrated hydrochloric acid (90ml) was added, the two solvent phases separated and the aqueous phase heated under reflux for 18h. The reaction mixture was evaporated to half volume, neutralised with solid potassium carbonate and extracted with dichloromethane. The material isolated from the organic extracts was chromatographed on silica in methanol-dichloromethane (1:9) to give the required azabicycle (250mg). δ (CDCl_3 , 360MHz) 1.75-1.80 (1H, m, H of CH_2); 2.06-2.12 (1H, m, H of CH_2); 2.70-2.81 (4H, m, $2 \times \text{NCH}_2$) and 3.00-3.12 (3H, m, COCH_2 and CH).

d) 3-(1,3-Dithian-2-ylidene)-1-azabicyclo-[2,2,1]heptane

A solution of n-butyl lithium in hexane (1.4ml of a 1.6M solution; 2.3mmol) was added to a solution of 2-trimethylsilyl-1,3-dithiane (457mg, 2.37mmol) in tetrahydrofuran (5ml) stirred under nitrogen at -35° . After 1.5h, the foregoing ketone

(220mg, 1.98mmol) in tetrahydrofuran (5ml) was added and the mixture allowed to warm to 20° over 1h. Water (20ml) was added and the solution extracted with dichloromethane. Chromatography of the material isolated from the organic extracts on alumina in methanol-dichloromethane (1:49) gave the dithioacetal ketene (370mg), δ (CDCl₃, 360MHz) 1.35-1.48 (1H, m, CH); 1.76-1.90 (2H, m, CH₂); 2.10-2.17 (2H, m, CH₂); 2.43 (1H, dd, J = 3Hz and 9Hz, bridge CH); 2.46-2.58 (1H, m, CH); 2.62 (1H, m, CHN); 2.70-2.94 (5H, m, CH and 2 x CH₂S); 3.02 (1H, dd, J = 3Hz and 18Hz, CH-C=C) and 3.41 (1H, dd, J = 3Hz and 18Hz, CH-C=C).

15 e) 3-Ethoxycarbonyl-1-azabicyclo[2,2,1]heptane

The foregoing vinyl dithiane (370mg, 1.74mmol) in ethanol (30ml) saturated with anhydrous hydrogen chloride was stirred at 50° for 16h. After evaporation of the solvent, the residue was partitioned between dichloromethane and water to which solid potassium carbonate was added to pH 10. Chromatography of the residue isolated from the organic layer on alumina in methanol-dichloromethane (1:19) gave the required ethyl ester (227mg), δ (CDCl₃, 360MHz) 1.25 (3H, t, J = 7Hz, CH₃); 1.8-3.3 (10H, m, 4 x CH₂ and 2 x CH); 4.12 (2H, q, J = 7Hz, OCH₂).

30 f) 3-[5-(3-Amino-1,2,4-oxadiazol)-yl]-1-azabicyclo[2,2,1]-heptane and hydrochloride salt

Sodium metal (210mg, 9.1mmol) was added to a suspension of powdered molecular sieve (2g) in ethanol (25ml) stirred under nitrogen at 20°.

Hydroxyguanidine hemisulphate hemihydrate (700mg, 2.6mmol) was then added and the mixture stirred for 15 min. After addition of a solution of the foregoing ester (220mg, 1.3mmol) in ethanol (3ml),
5 the mixture was heated under reflux for 3.5h. After removal of the molecular sieve by filtration, the solvent was evaporated and the residue partitioned between dichloromethane and water. The material isolated from the organic layer was purified by
10 chromatography on alumina in dichloromethane-methanol (24:1) followed by crystallisation from i-propanol-hexane to afford the required aminooxadiazole (60mg) as a mixture of exo and endo isomers, mp. 126-127°; (found: C, 53.0; H, 6.7; N, 30.4. $C_8H_{12}N_4O$. 0.1 H_2O requires C, 52.8; H, 6.7; N, 30.8%); m/e 180 (M^+); δ ($CDCl_3$, 360MHz) 1.27 (1H, broad s, CH of CH_2); 1.66-1.78 (1H, m, CH of CH_2); 2.39-3.40 (8H, m, 3 x CH_2 and 2 x CH) and 4.37 (2H, broad 2, NH_2).
20 Chromatography of the mixture of isomers (through silica gel) using dichloromethane/methanol (2:1) as eluant gave the two separated isomers as white crystalline solids. Isomer A the least polar and major component was treated with ethereal
25 hydrogen chloride to give the salt, mp. 230-232° (methanol/ether). [Found: C, 44.54; H, 5.72; N, 25.42 $C_8H_{13}N_4OCl$ requires C, 44.34; H, 6.00; N, 25.87%] δ (360 MHz, D_2O) 1.94-2.08 (1H, m, CH of CH_2); 2.22-2.31 (1H, m, CH of CH_2); 3.30-3.85 (8H, m, 2 x CH and 3 x CH_2 -N) and 4.8-4.9 (2H, brs, NH_2); m/e 180 (M^+). Isomer B Ethereal hydrogen chloride was added to isomer B to give the salt, mpt 214-216° (methanol/ether); [Found C, 44.50; H, 5.81;

N, 25.46. $C_8H_{13}N_4OCl$ requires C, 44.34; H, 6.00; N, 25.87%] δ (360MHz; D_2O) 1.65-1.74 (1H, m, \underline{CH} of CH_2); 2.08-2.15 (1H, m, \underline{CH} of CH_2); 3.36-3.57 (5H, m, \underline{CH} and 2 x CH_2-N); 3.66-3.71 (1H, m, 1 x \underline{CH} of CH_2-N); 3.86-4.01 (1H, m, \underline{CH} -oxadiazole) and 4.02-4.07 (1H, m, 1 x \underline{CH} of CH_2-N); m/e 180 (M^+)..

EXAMPLE 25

10 1-Methyl-3[5-(3-amino-1,2,4-oxadiazol)-yl]-1,2,5,6-tetrahydropyridine

Hydroxyguanidine hemisulphate hemihydrate (6.65g, 50mmol) was stirred with molecular sieve (type 4A, 10g) in ethanol (50ml) for 0.5h. Sodium (2.2g, 95mmol) was then added, stirring continued for 15 a further 0.5h when all the sodium had dissolved, and then arecoline hydrobromide (2.3g, 10mmole) added to the reaction mixture. After 0.5h at 20°, the mixture was heated under reflux for 0.5h, cooled and 20 neutralised by the addition of acetic acid (5.7g). After filtration, the filtrate was evaporated and the residue taken into the minimum quantity of saturated aqueous potassium carbonate solution. Exhaustive 25 extraction of this solution with dichloromethane followed by evaporation of the combined organic extracts gave the crude product which was purified by chromatography on alumina in ethyl acetate and then ethyl acetate-methanol (99:1). Evaporation of the single component fractions gave the required 30 oxadiazole (310mg), mp. 118-119°; (Found: C, 53.3; H, 6.8; N, 30.6. $C_8H_{12}N_4O$. $0.05H_2O$ requires C, 53.0; H, 6.7; N, 30.9%); m/e 180 (M^+); δ ($CDCl_3$, 360MHz) 2.45 (5H, broad s, NCH_2 and NCH_3); 2.58 (2H, t, $J = 5.7Hz$, NCH_2CH_2);

3.30-3.32 (2H, m, CH_2CH); 4.39 (2H, broad s, NH_2)
and 6.99-7.01 (1H, m, CH).

EXAMPLE 26

5

1-Methyl-3[5-(3-amino-1,2,4-oxadiazol)-yl] piperidine

This was prepared from ethyl 1-methyl piperidine-3-carboxylate using the procedure given in example 25. After chromatography the required
10 oxadiazole was crystallised from ethyl acetate-hexane, mp 72-73°; (Found: C, 50.4; H, 8.0; N, 29.2 $\text{C}_8\text{H}_{14}\text{N}_4\text{O}$. 0.4 H_2O requires C, 50.7; H, 7.9; N, 29.6%); m/e 182 (M^+); δ (CDCl_3 , 360MHz) 1.57-1.82 (4H, m, CH_2CH_2); 1.95-2.12 (2H, 15 m, NCH_2); 2.32 (3H, s, NCH_3); 2.69-2.78 (1H, m, CH); 3.01-3.13 (2H, m, NCH_2) and 4.30 (2H, broad s, NH_2).

EXAMPLE 27

20

6-[5-(3-Methyl-1,2,4-oxadiazol)-yl]-1-azabicyclo[3.2.1]octane Hydrochloride

This was prepared from 6-carbomethoxy-1-azabicyclo[3.2.1]octane and acetamideoxime according to
25 the procedure described for example 18. The hydrochloride salt had mp. 240-242°C (isopropyl-alcohol); (Found: C, 52.53; H, 6.93; N, 18.14; $\text{C}_{10}\text{H}_{16}\text{N}_3\text{O Cl}$ requires C, 52.29; H, 6.97; N, 18.30%); δ (360MHz, CDCl_3). 1.50-1.90 (4H, m, 2
30 x CH_2); 2.36 (3H, s, Me); 2.62 (1H, br s, CH -bridgehead); 2.80-2.94 (4H, m, 2 x CH_2 -N); 3.09 (1H, dd, J = 5.4; 13Hz, CH -N); 3.42-3.50 (1H, m, CH -N); 3.66 (1H, dd, J = 5.4, 8.6Hz, CH -oxadiazole).

EXAMPLE 282-[5-(3-Amino-1,2,4-oxadiazol)-yl]quinuclidine

Crushed molecular sieve (10g) and hydroxy-
5 guanidine hemisulphate hemihydrate (7.98g, 60mmole)
were stirred together in absolute ethanol (40ml)
under nitrogen for 0.5h. Sodium (12.53g, 110mmol) was
added in portions and stirring continued until all
the metal had dissolved. Ethyl quinuclidine-2-
10 carboxylate (11.83g, 10mmol) was added and the mixture
stirred at 20° for 0.5h and then at reflux
temperature for 1h. After cooling and filtering, the
solution was evaporated and the residue partitioned
between dichloromethane and a small amount of water.
15 The material isolated from the organic layer was
purified by chromatography or alumina in methanol-
dichloromethane (3:97) and then recrystallised from
ethyl acetate-hexane to afford the aminoxadiazole
(280mg), mp. 173-175°; (Found: C, 55.7; H, 7.2; N,
20 28.7 C₉H₁₄N₄O requires C, 56.0; H, 7.3; N,
29.0%); δ (CDCl₃, 360MHz) 1.52-1.71 (4H, m, 2 x
CH₂); 1.91-1.95 (1H, m, 4-CH); 2.00-2.04 (2H, m,
CH₂); 2.81-3.12 (4H, m, 2 x NCH₂); 4.09 (1H,
overlapping dd, each J = 8.6Hz, 2-CH) and 4.39 (2H,
25 broad s, NH₂).

EXAMPLE 293-Hydroxy-3-[5-(3-amino-1,2,4-oxadiazol)-yl]
30 quinuclidine

This was prepared from methyl 3-hydroxy-
quinuclidine-3-carboxylate using the procedure given
in example 25, except that the reaction time was 15

min. After filtration of the mixture and evaporation of the filtrate, the resulting solid was immediately purified by chromatography on alumina in methanol-dichloromethane (1:19) to give the desired

- 5 aminoxadiazole (220mg), mp 216-217°; (Found: C, 50.8; H, 6.6; N, 26.8. $C_9H_{14}N_4O_2 \cdot 0.1H_2O$ requires C, 51.1; H, 6.7; N, 26.5%); δ (d_6 -DMSO, 360MHz) 1.16-1.20, 1.27-1.36, 1.42-1.53 and 1.93-2.02 (each 1H, each m, 2 x CH_2); 2.11 (1H, broad s, 10 4-CH); 2.54-2.74 (4H, m, 2 x NCH_2); 2.77 and 3.48 (each 1H, each d, J = 14 Hz, 2 x NCH); 5.97 (1H, s, OH) and 6.26 (2H, broad s, NH_2).

EXAMPLE 30

15

2-[5-(3-Methyl-1,2,4-oxadiazol)-yl]-7-
azabicyclo[3,2,1]oct-2-ene Hydrochloride
 (a) 2-Carbomethoxy-7-aza-8-oxotricyclo
[4.2.1.0^{3,7}]nonane. Hydrochloride

20

The free base (2g, 0.01mol) was prepared by the procedure described by Tufariello (J. Amer. Chem. Soc., (1979), 101, 2435), and dissolved in anhydrous ether (50ml) at 0°C. Addition of 1.1 equiv of HCl dissolved in ether afforded a dense white
 25 precipitate. Filtration and recrystallisation from dichloromethane/ether afforded white crystals (1.8g) mp 150°C.

(b) 2-Carbomethoxy-1-hydroxy-7-azabicyclo
[3.2.1]octane

30

A solution of 1-carbomethoxy-7-aza-8-oxotricyclo[4.2.1.0^{3,7}]nonane hydrochloride (1.5g, 6.8mmol) was dissolved in methanol (40ml) to which was added a suspension of 10% palladium on

charcoal (0.3g) in methanol (5ml). The resulting suspension was shaken under an atmosphere of hydrogen (45psi) for 24 hours.

The catalyst was removed by filtration
5 through celite and the solvent evaporated at reduced pressure. The residue was dissolved in water (20ml), basified with 10% aqueous sodium carbonate, and extracted with dichloromethane (3 x 50ml). The combined extracts were dried (Na_2SO_4) and
10 evaporated, and the residue chromatographed through alumina using dichloromethane/methanol (95:5) as an eluant to afford the title compound as a colourless oil (11g) m/e 185 (M^+) δ (360MHz, CDCl_3)
1.2-1.9 (6H, m, 3 x CH_2); 2.85 (1H, dd, J 2.7,
15 5.9Hz, CHCO_2Me); 3.59 (1H, m, CHN); 3.75 (3H, s, CH_3); 3.85 (1H, m, CHN) and 3.93 (1H, m, CHOH).

(c) 2-[5-(3-Methyl-1,2,4-oxadiazol)-yl]-7-azabicyclo[3.2.1]oct-2-ene. Hydrochloride

Activated molecular sieves (Type 4A, 1g)
20 were added to a stirred solution of acetamide oxime (1.0g, 13.6mmol) in anhydrous tetrahydrofuran (30ml) under nitrogen. After 0.5hr, sodium hydride (0.5g of a 50% dispersion in oil, 11mmol) was added and the solution stirred for a further 0.5 hour. A solution
25 of 2-carbomethoxy-1-hydroxy-7-azabicyclo[3.2.1]octane (0.76g, 4.1mmol) in tetrahydrofuran (20ml) was then added and the resulting mixture heated at reflux for 2 hours. The reaction mixture was then cooled to room temperature diluted with water (100ml) and
30 extracted with ethyl acetate (5 x 50ml). The combined extracts were dried (MgSO_4), the solvent evaporated and the residue was chromatographed through alumina using dichloromethane/methanol (97:3)

as eluant to afford a pale yellow oil (0.48g). The product was further purified as the hydrochloride salt, mp. 239°(dec) (Ethanol); (Found: C, 52.3; H, 6.3; N, 18.3 $C_{10}H_{13}N_3O.HCl$ requires C, 52.7; H, 6.2; N, 18.4%); m/e 191 (M^+ of free base) δ (360MHz, D_2O) 7.11 (1H, t, =CH); 4.87 (1H, m, CH), 4.37 (1H, m, CH), 3.10 (1H, m, CHH); 2.64 (1H, m, CHH); 2.42 (3H, s, CH_3) and 2.4-1.95 (4H, m, 2 x CH_2).

10

EXAMPLE 31

3-[5-(3-Chloro-1,2,4-oxadiazol)-yl]quinuclidine
Hydrochloride

15 To a solution of 3-[5-(3-amino-1,2,4-oxadiazol)-yl]quinuclidine (4.0g, 20mmol) in concentrated hydrochloric acid (40ml) at 0°C was added dropwise sodium nitrite (2.0g, 30mmol) in water (1ml). After complete addition the solution was
20 stirred for 0.5h then filtered and concentrated under reduced pressure. The residue was treated with cold potassium carbonate solution which was extracted with dichloromethane. The dichloromethane solution was dried (Na_2SO_4) and then treated with ethereal HCl
25 to give the title compound as a white solid (3.36g); mp 179-182°C; (Found: C, 43.26; H, 5.29; N, 16.90. $C_9H_{13}Cl_2N_3O$ requires C, 43.22; H, 5.24; N, 16.80%); m/e 214 (FAB+, $[M+H]^+$ of free base); δ (360MHz, D_2O) 1.85-2.01 and 2.10-2.25 (each 2H, each m, 5 CH_2 and 8 CH_2), 2.66-2.72 (1H, m, 4CH),
30 3.35-3.52 (4H, m, 6 CH_2 and 7 CH_2); 3.77-3.90 and 3.95-4.02 (2H and 1H respectively, each m, 2 CH_2 and 3CH).

EXAMPLE 325-[5-(3-Methyl-1,2,4-oxadiazol)-ylquinuclidine-3-one5 a) cis Piperidine-3,4-dicarboxylic acid-3-methyl ester hydrochloride

Pyridine-3,4-dicarboxylic acid 3-methyl ester (5.00g, 27.6mmol), prepared by the method of J.C.S. Perkin I, 1981, 3012, in methanol (50ml) was treated
10 with excess ethereal hydrogen chloride and the solution evaporated to dryness. The resulting salt in methanol (100ml) was hydrogenated over platinum oxide (500mg) at 50 p.s.i. and ambient temperature until uptake ceased (24 h). The catalyst was removed
15 by filtration through Hyflo and the filtrate evaporated to give the title compound (6.17g, 100%), m.p. 180-184° (dec) δ (360MHz, D₂O) 2.10-2.20 (2H, m, 5-CH₂); 3.19-3.25 (2H, m, 3-CH, 4-CH); 3.27-3.32 (1H, m, 6-CH ax); 3.34-3.39 (1H, m, 6-CH
20 eq); 3.51 (1H,dd, J13Hz and 4Hz, 2-CH eq); 3.60 91H, dd, J 7.5 Hz and 13 Hz, 2-CH ax).

b) cis 1-t-Butoxycarbonylpiperidine-3,4-dicarboxylic acid 3-methyl ester

The foregoing piperidine salt (7.16g, 32.1
25 mmol) was dissolved in a solution of sodium carbonate (6.80g, 64.2mmol) in water (50ml) and a solution of di-t-butyl dicarbonate (8.39g, 38.5 mmol) in dioxan (15ml) added and stirred at room temperature 20 h. The solution was washed with ether, the aqueous layer
30 acidified with 2M citric acid, then extracted twice with ethyl acetate. The extracts were washed in turn with water and brine, dried over magnesium sulphate and evaporated to give the product 7.78g, 84%. m.p.

129-136°; (Found: C, 54.32; H, 7.19; N, 4.94.

$C_{13}H_{21}NO_6$ requires C, 54.35; H, 7.37; N, 4.88%; m/e (CI^-) 286 ($M-H^-$) γ max 3200 (br).

1740, 1700 (sl), 1655 cm^{-1} δ (360MHz, $CDCl_3$)

5 1.44 (9H, s, tBu); 1.89 (1H, br, 5-CH); 2.13 (1H, br, 5-CH); 2.84-2.89 (1H, m, 4-CH); 2.93-2.96 (1H, m, 3-CH); 3.12-3.21 (1H, m, 6-CH); 3.43-3.48 (1H, m, 6-CH); 3.68-3.75 (1H, m, 2-CH); 3.69 (3H, s, OCH_3) 4.07-4.14 (1H, m, 2-CH).

10 c) Methyl-1-t-butoxycarbonyl-4-diazomethyl carbonylpiperidine-3-carboxylate

The foregoing piperidine monoester (5.0g, 17.4mmol) was added to a suspension of sodium hydride (0.57g of 80% dispersion, 19.1mmol) in dry
15 tetrahydrofuran (50ml) and stirred at 25° until gas evolution ceased (2 h). Thionyl chloride (2.28g, 19.2mmol) was added and the mixture heated to 60° for 1 h. The cooled mixture was added dropwise to an ice-cooled ethereal solution of diazomethane,
20 generated from N-methyl-N-nitroso-p-toluene-sulphonamide (26.9g, 125mmol) by standard methods, and allowed to stand overnight. The solvent was evaporated, the residue partitioned between sodium hydrogen carbonate and dichloromethane, and the
25 organic layer dried and evaporated. Column chromatography on silica in dichloromethane/ethyl acetate (4:1) afforded the pure diazoketone as a yellow gum (3.4g, 63%). γ max 2120, 1740, 1690, 1640 cm^{-1} δ (360MHz, $CDCl_3$) 1.44 (9H, s, t-Bu);
30 1.76 (1H, br, 5-CH); 2.01-2.14 (1H, m, 5-CH); 2.81 (1H, br) and 2.88-2.98 (1H, m, 3-CH and 4-CH); 3.22-3.34 (1H, m, 6-CH); 3.50-3.71 (2H, m, 2-CH and 6-CH); 3.68 (3H, s, OCH_3); 4.02-4.11 (1H, m, 2-CH); 5.36 (1H, s, $CH=N_2$).

d) Methyl 5-oxoquinuclidine-3-carboxylate

To a solution of the foregoing diazoketone (529mg, 1.70mmol) in dichloromethane (25ml) at 0° was added hydrogen bromide in acetic acid (1.0ml of 48% w/v) and the solution stirred for 30 min. The solvent was removed using a toluene azeotrope to give methyl-4-bromomethylcarbonylpiperidine-3-carboxylate hydrobromide as a gum. δ (360MHz, D₂O) 2.01-2.22 (2H, m, 5-CH₂); 3.16-3.33 (2H, m, 3-CH, 4-CH); 3.40-3.58 (3H, m, 2-CH, 6-CH₂); 3.72-3.78 (1H, m, 2-CH); 3.73 (3H, s, OCH₃); 4.46 (2H, s, CH₂Br). This material in dry acetonitrile (200ml) was added dropwise to boiling acetonitrile (500ml) containing diisopropylethylamine (5.0ml, 29mmol) over 7 h, and refluxing continued for a further 1 h. The solvent was evaporated and the residue in 2M potassium carbonate extracted with dichloromethane. The extracts were dried, evaporated and purified by chromatography on silica in 5% methanol in dichloromethane to give the quinuclidine (120mg, 39%) as an 80:20 mixture of diastereoisomers in which the R*R* configuration predominates. m/e 183 (M⁺). γ max 1740cm⁻¹. δ (360MHz, CDCl₃) 2.01-2.07 (2H, m, 8-CH₂); 2.69 (1H, q, J 3Hz, 4-CH); 2.88-2.97 (2H, m, 7-CH₂); 3.03-3.10 (1H, m, 3-CH); 3.14-3.25 (2H, m, 2-CH₂); 3.32 (1H, d, J 10Hz, 6-CH); 3.39 (1H, d, J 10Hz, 6-CH); 3.69 (3H, s, OCH₃).

e) 5-[5-(3-Methyl-1,2,4-oxadiazol)yl]-quinuclidin-3-one

A solution of acetamide oxime (570mg, 7.7mmol) in dry THF (50ml) containing powdered 4A molecular sieve (1.5g) was stirred at 20° for 30 min.

then sodium hydride (230mg of 80% dispersion, 7.7mmol) added. The mixture was heated to reflux for 15 min, cooled, and the foregoing quinuclidine ketoester (1.08g, 5.9mmol) in THF (10ml) added. The solution was stirred for 15 min at 20°, then 1h at reflux. The cooled mixture was filtered through Hyflo, the filtrate evaporated and partitioned between 2M potassium carbonate and dichloromethane. The organic layer was dried, evaporated and purified by chromatography on silica in 10% methanol in ethyl acetate, to give isomer A (first eluted) (127mg) and isomer B (125mg). Isomer A (R*S*) was recrystallised from ethyl acetate-ether, m.p. 85-86.5°; (Found: C, 57.82; H, 6.23; N, 20.41. $C_{10}H_{13}N_3O_2$ requires C, 57.96; H, 6.32; N, 20.28%); m/e (CI) 208 ($M+H^+$); γ max 1740 cm^{-1} . δ (360MHz, $CDCl_3$) 1.84-1.96 (1H, m, 8-CH); 2.08-2.19 (1H, m, 8-CH); 2.43 (3H, s, CH_3); 2.87 (1H, q, J 3Hz, 4CH); 2.89-3.00 (1H, m, 7-CH); 3.09-3.20 (1H, m, 7-CH); 3.39 (2H, s, 2- CH_2); 3.44 (1H, dd, J14Hz and 2Hz, 6-CH); 3.52 (1H, dd, J14Hz and 6Hz, 6-CH); 3.60-3.64 (1H, m, 5-CH).

Isomer B (R*R*) was recrystallised from ethyl acetate m.p. 94-95° (Found: C, 58.04; H, 6.28; N, 20.50. $C_{10}H_{13}N_3O_2$ requires C, 57.96; H, 6.32; N, 20.28%); m/e (CI) 208 ($M+HH^+$); γ max 1740; δ (360MHz, $CDCl_3$): 2.08-2.24 (2H, m, 8- CH_2); 2.36 (3H, s, CH_3); 2.78 (1H, q, J3Hz, 4-CH); 2.95-3.10 (2H, m, 7- CH_2); 3.32-3.38 (1H, m, 6-CH); 3.39 (1H, d, J19Hz, 2-CH); 3.46-3.51 (1H, m, 6-CH); 3.51 (1H, d, J19Hz, 2-CH); 3.66-3.72 (1H, m, 5-CH).

The intermediate methyl 5-oxoquinuclidine-3-carboxylate required in this preparation was also synthesised by the following sequence:

a) N,N-Diethyl 4-Methoxycarbonylpyridine

5 3-carboxamide

Sodium hydride (6.6g of 80% dispersion, 0.22mol) was washed with hexane, suspended in dry tetrahydrofuran (500ml) under nitrogen and solid pyridine-3,4-dicarboxylic acid 4-methyl ester, 10 (36.2g, 0.20mol; prepared by the method of J.C.S. Perkin I. (1981) 3012) added portionwise. The mixture was stirred at 25° for 1 h, then at reflux for 30 min and cooled. Thionyl chloride (16.0ml, 0.22 mol) was added and stirring continued at 25° for 15 1 h and at 70° for 30 min. The solution was cooled and diethylamine (43.8g, 0.60 mol) added. After standing overnight, 2M potassium carbonate was added and the product extracted with dichloromethane. Evaporation of the organic layers gave the ester 20 amide as an orange oil (44.7g) which was used in the next step without purification. m/e (CI) 237 (M+H⁺); δ (CDCl₃) 1.08 and 1.30 (each 3H, t, J7Hz, 2 x CH₂CH₃); 3.13 and 3.61 (each 2H, q, J7Hz, 2 x CH₂CH₃); 3.91 (3H, s, OCH₃); 7.82 25 (1H, d, J5Hz, 5-CH); 8.61 (1H, s, 2-CH) and 8.75 (1H, d, J5Hz, 6-CH).

b) N,N-Diethyl 4-Methoxycarbonyl-1-methoxycarbonyl methyl pyridinium-3-carboxamide bromide

30 The foregoing pyridine ester amide (23.6g, 0.10 mol) and methyl bromoacetate (15.3g, 0.10 mol) were heated in methanol under reflux for 24 h and the

solvent evaporated. The residue in water was washed with dichloromethane and the aqueous layer evaporated to dryness to give the desired pyridinium salt which crystallised on standing (36.9g). m.p. 133-134° (dec) δ (DMSO) 0.95 and 1.10 (each 3H, t, J7Hz, 2 x

- 5 CH_2CH_3); 3.37 and 3.39 (each 2H, q, J7Hz, 2 x CH_2CH_3); 3.70 and 3.84 (each 3H, s, 2 x OCH_3); 5.67 (2H, s, CH_2CO_2); 8.56 (1H, d, J6Hz, 5-CH); 9.20 (1H, d, J6Hz, 6-CH); 9.31 (1H, s, 2-CH).

10 c) Cis N,N-Diethyl 4-Methoxycarbonyl-1-methoxycarbonylmethyl piperidine-3-carboxamide

- The foregoing crude pyridinium salt (36.0g, 0.093 mol) was treated with Raney nickel in methanol (200ml) to remove sulphur containing impurities and filtered. The filtrate was hydrogenated over
15 platinum oxide (600mg) at 50 psi and 50° until uptake ceased (72h). The solution was filtered through Hyflo, evaporated and partitioned between 2M potassium carbonate and dichloromethane. Chromatography of the residue from the organic layer on silica in 3%
20 methanol in dichloromethane gave the desired piperidine (9.0g) as an oil. m/e (CI) 315 ($\text{M}+\text{H}^+$); δ (CDCl_3) 1.09 and 1.22 (each 3H, t, J7Hz, 2 x CH_2CH_3); 1.92-2.01 (1H, m, 5-CH ax); 2.25-2.34 (1H, m, 5-CH eq); 2.60-2.66 (2H, m, 4-CH, 6-CH); 2.75
25 (1H, dd, J4Hz, 11Hz, 3-CH); 2.84-2.90 (1H, m, 6-CH); 2.99 (1H, dd, J8Hz, 11Hz, 2-CH ax); 3.16-3.21 (1H, m, 2-CH, eq); 3.28-3.43 (6H, m, 2 x CH_2CH_3 , CH_2CO_2) and 3.66 and 3.70 (each 3H, s, 2 x OCH_3).

30 d) Methyl 5-Oxoquinuclidine-3-carboxylate

A suspension of molten potassium (2.63g, 67.5 mol) in dry toluene (70ml) was heated in an oil bath at 120° whilst stirring vigorously with a

Hirschberg stirrer, and methanol (3.0ml, 73mmol) was added dropwise. After 30 min, the bath temperature was raised to 140° and the foregoing piperidine (8.5g, 27.0mol) in toluene (20ml) added dropwise over
5 15 min. Heating and stirring was continued for 2 h, then mixture cooled in ice and concentrated hydrochloric acid (100ml) added. The toluene layer was separated, washed with more hydrochloric acid (60ml), and the combined acid layers heated under
10 reflux for 16 h. The cooled solution was evaporated to dryness, using a toluene azeotrope, then the residue was suspended in methanol (400ml) and dry hydrogen chloride passed in for 2 h. The solution was stirred at 25° for 2 days, filtered, evaporated
15 and partitioned between 2M potassium carbonate and dichloromethane. Chromatography of the residue from the organic layer on silica in 2% methanol in dichloromethane yielded the desired keto ester (488mg), identical in all respects with that obtained
20 by the route given above.

EXAMPLE 33

25 5-[5-(3-Methyl-1,2,4-oxadiazol)-yl]quinuclidin-3-ol

To a solution of 4R*5S* 5-[5-(3-methyl-1,2,4-oxadiazol)-yl]quinuclidin-3-one (isomer A) 400mg, 1.93mmol) in ethanol (20ml) at 0° was added sodium
30 borohydride (146mg, 3.86mmol) and the solution stirred for 1 h. Excess borohydride was destroyed with 2M hydrochloric acid, then the solution basified with 2M potassium carbonate and the product extracted

with dichloromethane, dried and evaporated. Chromatography on alumina in 1% methanol in dichloromethane did not separate the two epimeric alcohols, but gave the title compound (270mg) as a
5 64:36 mixture, H.P.L.C. retention times 6.60, 7.37 min on Spherisorb C1 in 50mM phosphate, 0.2% triethylamine, pH 6.5-acetonitrile 90:10. m.p. 112-114.5 (Found: C 56.87; H, 7.10; N, 19.57; $C_{10}H_{15}N_3O_2 \cdot 0.1H_2O$ requires C, 56.91; H, 7.26; N, 19.91%); m/e (CI) 210 ($M+H^+$); ν_{max} 3500-2500 (br), 1575 cm^{-1} ; δ (360MHz, $CDCl_3$): 1.32-1.50 (1H, m, 8-CH); 1.68-1.98 (2H, m, 8-CH and OH); 2.29-2.34 (1H, m, 4-CH); 2.40 (3H, s, CH_3); 2.63-2.76 (2H, m, 7- CH_2); 2.88-2.97 (2H, m, 2-CH, 6-CH); 3.05-3.28 (3H, m, 2-CH, 5-CH, 6-CH); 4.03-4.09 (1H, m, 3-CH).

The 4R*5R* isomer of the starting quinuclidinone (381mg, 1.84mmol) was treated in exactly the same way to yield the title alcohol (284mg) as
20 15:85 mixture, HPLC retention times 3.67, 4.04 min on Spherisorb-NH₂ in acetonitrile-water 80:20. m.p. 150-155° (Found: C, 57.26; H, 7.04; N, 19.73; $C_{10}H_{15}N_3O_2$ requires C, 57.40; H, 7.23; N, 20.08%); m/e (CI) 210 ($M+H^+$); ν_{max} 3500-2500 (br), 1570 cm^{-1} ; δ (360MHz, $CDCl_3$): 1.55-1.64 (1H, m, 8-CH); 1.75-1.84 (1H, m, 8-CH); 2.38 (3H, s, CH_3); 2.54-2.59 (1H, m, 4-CH); 2.75-2.84 (3H, m, 7- CH_2 , 6-CH); 3.12-3.49 (5H, m, 2- CH_2 , 5-CH, 6-CH, OH); 3.88-3.92 (1H, m, 3-CH).

EXAMPLE 34

5-Methyl-3-[5-(3-methyl-1,2,4-oxadiazol)-yl]
quinuclidine

5 a) Methyl 5-Methylenequinuclidine-3-
 carboxylate

Methyl triphenylphosphonium iodide (2.97g, 7.35mmol) and potassium t-butoxide (0.83g, 7.35mol) in dry tetrahydrofuran (40ml) was heated under reflux for 1.5 h, then cooled to 0° and methyl 5-oxo quinuclidine-3-carboxylate (see Example 32d) (1.17g, 6.39mmol) in tetrahydrofuran (5ml) added. The mixture was stirred at 0° for 1 h, at 20° for 1 h then partitioned between 2M potassium carbonate solution and dichloromethane. The material obtained from the organic layer was purified by chromatography on silica in 5% methanol in dichloromethane to give the desired methylene quinuclidine as a colourless gum (0.746g); m/e 181 (M^+); δ (360MHz, $CDCl_3$) 1.60--1.68 (1H, m, 8-CH); 1.78-1.87 (1H, m, 8-CH); 2.77-2.92 (1H, m, 7-CH); 2.82-2.85 (1H, m, 4-CH); 3.00-3.17 (2H, m, 3-CH, 7-CH); 3.26 (1H, d, J13Hz, 2-CH); 3.43 (1H, dd J13Hz, 5Hz, 2-CH); 3.56 (2H, s, 6-CH₂); 3.75 (3H, s, OCH₃); 4.82 (1H, s, C=CH) and 5.13 (1H, s, C=CH).

b) Methyl 5-Methylquinuclidine-3-
carboxylate

The foregoing methylene quinuclidine (745mg, 4.12mmol) in methanol (60ml) was hydrogenated over 10% palladium on carbon (100mg) at 50 p.s.i. and 25° until uptake ceased. Filtration through Celite and evaporation yielded the methyl quinuclidine (579mg) as a mixture of two diastereoisomers, which was used

in the next step without purification; m/e 183 (M^+); δ (360MHz, $CDCl_3$) 1.04 and 1.05 (each d, J7Hz, CH_3); 1.36-1.45 (1H, m, 8-CH) 1.58-1.85 (2H, m, 5-CH, 8-CH); 1.91-1.95 (1H, m, 4-CH); 2.18-2.31 (1H, m, 3-CH); 2.66-3.33 (6H, m, 2- CH_2 , 6- CH_2 , 7- CH_2) and 3.71 and 3.72 (3H, each s, OCH_3).

c) 5-Methyl-3-[5-(3-methyl-1,2,4-oxadiazol)-yl]quinuclidine

A solution of acetamide oxime (304mg, 4.11mmol) in dry tetrahydrofuran (30ml) containing powdered 4A molecular sieve (1.0g) was stirred for 1 h, sodium hydride (99mg of 80% dispersion, 4.11 mmol) added, and the mixture heated under reflux for 15 min. After cooling to 25°, the foregoing methyl 5-methylquinuclidine-3-carboxylate (575mg, 3.15mmol) in tetrahydrofuran (9ml) was added and stirring continued for 30 min at 25° and 40 min at reflux. The cooled solution was filtered through Celite, evaporated to dryness and partitioned between 2M potassium carbonate and dichloromethane. Chromatography of the material obtained from the organic layers on alumina in 2% methanol in dichloromethane yielded the title compound (340mg) as a mixture of all four diastereoisomers, ratio 16:48:11:25 by capillary g.c., 25m BP10, 170°, RT 11.05, 11.17, 11.40, 11.89 min. The mixture was converted to the hydrochloride, mp 152-158° (softens at 130°); [Found: C, 52.9; H, 7.3; N, 16.3. $C_{11}H_{17}N_3O \cdot HCl \cdot 0.45 H_2O$ requires C, 52.5; H, 7.6; N, 16.7%]; m/e 207 (M^+ , free base); δ (360 MHz, D_2O) 0.62, 1.08, 1.20, 1.23 (3H, each d, J7Hz, 5- CH_3); 1.91-1.96 (1H, m, 8-CH); 2.05-2.23 (1H, m, 8-CH); 2.41-2.50 (2H, m, 4-CH, 5-CH); 2.42 (3H, s,

Ar CH₃); 2.82-2.96 (1H, m, 3-CH); 3.31-3.45 (2H, m, 7-CH₂) and 3.59-4.08 (4H, m, 2-CH₂, 6-CH₂).

EXAMPLE 35

5

5-[5-(3-Methyl-1,2,4-oxadiazol)-yl]
quinuclidine-3-carboxylic acid Hydrochloride

a) 3-(1,3-Dithian-2-ylidene)-5-[5-(3-methyl-
1,2,4-oxadiazol)-yl]quinuclidine

10 n Butyl lithium (5.5ml of 1.5M solution,
8.29 mmol) was added to a stirred solution of
2-trimethylsilyl-1,3-dithian (1.59g, 8.29mmol) in dry
tetrahydrofuran at -30° under nitrogen. After 1 h
5-[5-(3-methyl-1,2,4-oxadiazol)-yl]quinuclidine-3-
15 one (see Example 32), as a mixture of diastereo-
isomers, (1.56g, 7.54mmol) in tetrahydrofuran (10ml)
was added, and after 20 min at -30°, the solution was
allowed to warm to 25° over 1 h. Water (20ml) was
added, and extracted three times with
20 dichloromethane. Chromatography of the material
obtained from the organic extracts on silica in 5%
methanol in ethyl acetate yielded one diastereoisomer
("A") of the pure product (80mg) and the other as a
mixture (712mg). Diastereoisomer A (obtained pure)
25 had m/e 309 (M⁺); δ (CDCl₃) 1.48-1.57 (1H, m,
8-CH); 1.72-1.81 (1H, m, 8-CH); 2.15-2.22 (2H,
quintet, J6Hz, SCH₂CH₂); 2.41 (3H, s, CH₃);
2.77-3.05 (7H, m, 4-CH, 7-CH₂, 2 x SCH₂);
2.24-3.31 (1H, m, 6-CH); 3.37-3.43 (1H, m, 6-CH);
30 3.56 (2H, s, 2-CH₂) and 3.55-3.58 (1H, m, 5-CH).

b) Methyl 5-[5-(3-Methyl-1,2,4-oxadiazol)-
yl]quinuclidine-3-carboxylate

A solution of the foregoing dithian (88mg,

0.28 mmol) in methanol saturated with hydrogen chloride (10ml) was stirred at 25° for 24 h and the solvent evaporated. The residue in 2M potassium carbonate was extracted with dichloromethane.

5 Chromatography of the residue from the organic extracts on silica in 5% methanol in dichloromethane gave the ester as a mixture of diastereoisomers (45mg); [Found: CI^- mass spectrum: $\text{M}-\text{H}^-$, 250.1192. $\text{C}_{12}\text{H}_{16}\text{N}_3\text{O}_3$ requires $\text{M}-\text{H}^-$, 250.1192); m/e (CI) 251 (M^+). δ 1.43-1.51 (1H, m, 8-CH); 1.68-1.81 (1H, m, 8-CH); 2.40, 2.41 (3H, 2 x s, Ar CH_3); 2.57-2.62 (1H, m, 4-CH); 2.70-2.95 (4H, m, 3-CH, 5-CH, 7- CH_2); 3.13-3.41 (4H, m, 2- CH_2 , 6- CH_2); 3.74, 3.76 (3H, 2 x s, OCH_3).

15 c) 5-[5-(3-Methyl-1,2,4-oxadiazol)-yl]quinuclidine-3-carboxylic acid. Hydrochloride

The title compound was obtained as a mixture of diastereoisomers by treating the foregoing ester with 6M hydrochloric acid at 25° for 24 h followed by
20 evaporating to dryness.

EXAMPLE 36

25 5-[5-(3-Methyl-1,2,4-oxadiazol)-yl]quinuclidine-2-carboxylic. Acid Hydrochloride

a) Methyl-5-Methoxymethylenequinuclidine-2-carboxylate

n-Butyllithium (13.67ml of a 1.5M solution; 20.5mmol) was added at 20° to a suspension of
30 methoxymethyltriphenyl phosphonium chloride (7g, 20.5mmol) stirred in ether (150ml) under nitrogen. After 2h, the mixture was cooled to -35° and a solution of methyl 5-oxoquinuclidine-2-carboxylate

(3g, 16.4mmol; prepared as described in Zhur. Obshechi. Khim., (1960), 30, 519; see Chem. Abs. (1960), 54: 24723) in ether (20ml) added. The mixture was allowed to warm to 20° over 1h and then stirred at this temperature for 16h. After removing the precipitated triphenylphosphine oxide by filtration, the ether was evaporated off and the resulting oil subjected to chromatography on silica in 3% methanol in dichloromethane to afford the title compound (2.05g) as a mixture of isomers; m/e 211 (M^+); δ (360MHz, $CDCl_3$) 1.2-2.0 (4H, m, 2 x CH_2); 2.18-2.34 (1H, m, 4-CH); 2.5-3.4 (5H, m, 2 x NCH_2 and NCH); 3.50-3.56 (3H, m, OCH_3); 3.78-3.82 (3H, m, CO_2CH_3) and 5.73-5.83 (1H, m, CH).

15 b) Methyl 5-Formylquinuclidine-2-carboxylate

The foregoing enol-ether (3.6g) in chloroform (50ml) was treated at 20° with perchloric acid (40ml) for 3h. The chloroform layer was discarded and replaced by dichloromethane (50ml). Water (50ml) and then solid sodium carbonate was added cautiously to the mixture until the pH reached 9.5. Evaporation of the organic phase gave the desired aldehyde, (2.76g); [Found: (high resolution mass spectrum) $M^+ = 197.1057 C_{10}H_{15}NO_3$ requires $M^+ = 197.1052$]; δ ($CDCl_3$ 360MHz) 1.5-2.6 (5H, m, 2 x CH_2 and 4-CH); 2.8-3.6 (6H, m, 2 x NCH_2 , 2-CH and 5-CH); 3.75-3.81 (3H, m, OCH_3) and 9.75-9.81 (1H, m, CHO).

25 c) Methyl 5-[5-(3-Methyl-1,2,4-oxadiazol)yl] quinuclidine-2-carboxylate

30 The foregoing aldehyde (1.18g, 6mmol) in 1M sulphuric acid (5ml, 5mmol) at 15° was treated with aqueous potassium permanganate solution (40ml of a 0.1M solution, 4mmol) added dropwise over 15 min.

After a total time of 1h, the reaction mixture was filtered through hyflo and the resulting aqueous solution freeze dried over 16h. The resulting powder was heated under reflux in thionyl chloride (20ml)

5 for 3h and then evaporated to dryness.

Re-evaporation after the addition of toluene gave a gum which was taken up in dimethylformamide (10ml) to which acetamide oxime (370mg, 5mmol) was added.

After 1h at 60° and 16h at 120°, the reaction mixture
10 was again evaporated to dryness and the residue partitioned between dichloromethane and water to which excess potassium carbonate was added. The material isolated from the organic layer was purified by chromatography on silica in 5% methanol in
15 dichloromethane to afford the oxadiazole as a mixture of isomers (140mg); [Found: (high resolution mass spectrum) $M^+ = 251.1268$. $C_{12}H_{17}N_3O_3$ requires $M^+ = 251.1270$]; δ ($CDCl_3$, 360MHz) 1.25-2.09 (4H, m, 2 x CH_2); 2.28-2.54 (4H, m, CH_3
20 and 4-CH); 2.90-3.69 (6H, m, 2 x NCH_2 , 2-CH and 5-CH) and 3.77-3.82 (3H, m, OCH_3).

d) 5-[5-(3-Methyl-1,2,4-oxadiazole)-yl]-quinuclidine-2-carboxylic Acid. Hydrochloride

All of the foregoing ester was treated with
25 6N-hydrochloric acid at 25° for 16h to give the title compound as a mixture of diastereomers.

EXAMPLE 37

30 5-[5-(3-Amino-1,2,4-oxadiazol)-yl]-quinuclidine-3-ol Hydrogen Oxalate

a) 5-[5-(3-Amino-1,2,4-oxadiazol)-yl]-quinuclidine-3-one

A suspension of hydroxyguanidine hemisulphate hemihydrate (1.15g, 8.67mmol) and powdered 4A molecular sieve (5g) in ethanol (50ml) was stirred for 1h, then sodium (0.38g, 16.7mmol) was added, and the mixture heated under reflux for 20 min and cooled. A solution of methyl 5-oxoquinuclidine-3-carboxylate (1.22g, 6.67mmol) (see Example 32) in ethanol (15ml) was added and stirred for 30 min at 25°, 30 min at reflux and recooled in an ice bath. Acetic acid (0.5ml) was added and the solution filtered through Hyflo. The filtrate was basified with aqueous potassium carbonate and evaporated to dryness. The residue was extracted with ethanol and the solvent removed. Chromatography of the material obtained on silica in 10% methanol in dichloromethane yielded the amino oxadiazole (107mg) as a 3:1 mixture of diastereoisomers; [Found: (CI⁻ high resolution mass spectrum); (M-H)⁻ = 207° 0869. C₉H₁₁N₄O₂ requires (M-H)⁻ = 207.0882]; δ (CDCl₃) 2.08-2.14 (2H, m, 8-CH₂); 2.76-2.79 and 2.84-2.87 (1H, each m, 4-CH of two diastereoisomers); 2.93-3.08 (2H, m, 7-CH₂); 3.25-3.32 (1H, m, 6-CH); 3.36-3.52 (3H, m, 2-CH₂, 6-CH); 3.56-3.62 (1H, m, 5-CH); 4.29-4.46 (2H, br, NH₂).

25 b) 5-[5-(3-Amino-1,2,4-oxadiazol)-yl] quinuclidine-3-ol. Hydrogen Oxalate

The foregoing quinuclidine (100mg, 0.48mmol) in ethanol (5ml) was treated with sodium borohydride (25mg, 0.66mmol) at 25° for 40 min. Excess borohydride was destroyed by dropwise addition of 2M hydrochloric acid, then the solution basified with 2M potassium carbonate and evaporated to dryness. The

The residue was extracted twice with boiling ethanol and the extracts filtered and evaporated. Chromatography of the material obtained on alumina in 5% methanol in dichloromethane yielded the desired alcohol as a mixture of all four diastereoisomers (65mg), which was characterised as the hydrogen oxalate salt. m.p. 48-55° [Found: m/e (CI⁻); (M-H)⁻ = 209.1034. C₉H₁₃N₄O₂ requires (M-H)⁻ = 209.1039]; δ (D₂O): 1.81-2.00 (2H, m, 8-CH₂); 2.65-2.74 (1H, m, 4-CH); 3.14-3.41 (2H, m, 7-CH₂); 3.65-3.84 (4H, m, 2-CH₂, 6-CH₂); 4.01-4.19 (1H, m, 5-CH); 5.42-5.51 (1H, m, 3-CH).

EXAMPLE 38

Tablet Preparation

Tablets containing 1.0, 2.0, 25.0, 26.0, 50.0 and 100.0 mg., respectively, of the following compounds are prepared as illustrated below:

- 3-[5-(3-amino-1,2,4-oxadiazol)-yl]quinuclidine;
5-[5-(3-amino-1,2,4-oxadiazol)-yl]quinuclidin-3-ol;
1-methyl-3-[5-(3-amino-1,2,4-oxadiazol-yl)pyrrolidine;
3-[5-(3-amino-1,2,4-oxadiazol)-yl]-1-azabicyclo[2,2,1]heptane.

TABLE FOR DOSES CONTAINING FROM

1-25 MG OF THE ACTIVE COMPOUND

5

Amount-mg.

10

Active Compound	1.0	2.0	25.0
Microcrystalline cellulose	49.25	48.75	37.25
Modified food corn starch	49.25	48.75	37.25
Magnesium stearate	0.50	0.50	0.50

15

TABLE FOR DOSES CONTAINING FROM

26-100 MG OF THE ACTIVE COMPOUND

20

Amount - mg.

Active Compound	26.0	50.0	100.0
25 Microcrystalline cellulose	52.0	100.0	200.0
Modified food corn starch	2.21	4.25	8.5
Magnesium stearate	0.39	0.75	1.5

30

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All of the active compound, lactose, and a
portion of the corn starch are mixed and granulated
to a 10% corn starch paste. The resulting
5 granulation is sieved, dried and blended with the
remainder of the corn starch and the magnesium
stearate. The resulting granulation is then
compressed into tablets containing 1.0 mg, 2.0 mg,
25.0 mg, 26.0 mg, 50.0 mg, and 100.0 mg of active
10 ingredient per tablet.

15

20

25

30

A

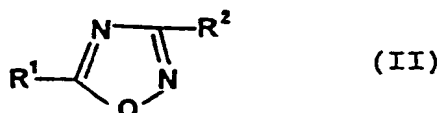
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CLAIMS for the designated states: DE, GB, FR, IT, NL, SE, CH, BE, LU

1. An oxadiazole compound, substituted on one of the ring carbon atoms thereof with a
5 non-aromatic azacyclic or azabicyclic ring system; and substituted on the other ring carbon with a substituent of low lipophilicity, or a salt thereof.

2. A compound as claimed in Claim 1 having
10 the formula (II):



15 or a pharmaceutically acceptable salt thereof; wherein R¹ represents a non-aromatic azacyclic or azabicyclic ring system; and R² represents a substituent of low lipophilicity.

20 3. A compound as claimed in either Claim 1 or Claim 2 wherein the azabicyclic ring system is a pyrrolidine, quinuclidine or 1-azabicyclo[2,2,1] heptane ring, optionally substituted with methyl or
25 hydroxy.

4. A compound as claimed in any one of
Claims 1 to 3 wherein the substituent of low
lipophilicity is hydrogen, methyl, amino,
30 methoxycarbonyl or ethoxycarbonyl.

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5. A compound as claimed in Claim 2 wherein R² represents amino.

6. A compound as claimed in Claim 1 which
5 is: 3-[5-(3-amino-1,2,4-oxadiazol)-yl]quinuclidine;
5-[5-(3-amino-1,2,4-oxadiazol)-yl]quinuclidin-
3-ol;
1-methyl-3-[5-(3-amino-1,2,4-oxadiazol)-yl]
pyrrolidine;
10 3-[5-(3-amino-1,2,4-oxadiazol)-yl]-1-azabicyclo
[2,2,1]heptane.

7. A pharmaceutical composition which
comprises a pharmaceutically acceptable carrier and a
15 compound as claimed in any one of Claims 1 to 6.

8. A pharmaceutical composition as claimed
in Claim 7 which further comprises a peripheral
cholinergic antagonist.
20

9. The use of a compound as claimed in any
one of Claims 1 to 6 for the preparation of a
medicament for the treatment of neurological and
mental disorders.
25

10. A process for the preparation of a
compound as claimed in Claim 1, which process
comprises reacting a reactive derivative of a
30

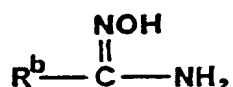
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carboxylic acid of formula R^aCO_2H , with either a compound of formula (IIIA) or (IIIB) or a salt thereof:

5



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(IIIA)

(IIIB)

wherein one of R^a and R^b is a non-aromatic azacyclic or azabicyclic ring system, and the other is a group of low lipophilicity.

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11. A process for the preparation of a compound as claimed in Claim 1, which process comprises:

20

a) reacting a compound of formula (IV): $R^a-CO-N=C(R^b)N(CH_3)_2$, with hydroxylamine;

b) oxidizing an oxadiazoline with an oxidizing agent;

25

c) when the non-lipophilic substituent is amino, reacting a compound of formula (IIIA) with a cyanogen halide;

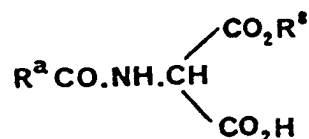
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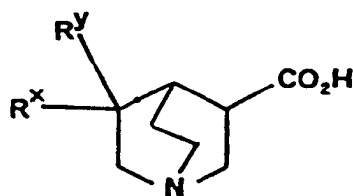
d) when the non-lipophilic substituent is
(C₁₋₃) alkoxycarbonyl, reacting a compound of formula:



with nitrous acid;

e) when the desired product is a
1,3,4-oxadiazole, reacting a compound of formula
15 $\text{R}^a\text{CO.NH.NH.CO.R}^b$, with a dehydrating agent, at an
elevated temperature.

12. An intermediate of formula (V):



(V)

or a reactive derivative thereof, wherein R^X
30 represents H and R^Y represents hydroxy, or R^X and R^Y
together represent oxygen.

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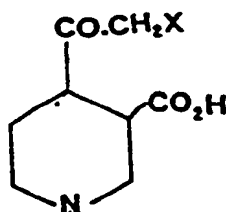
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13. A process for the preparation of a compound as claimed in Claim 12 which comprises cyclisation of a compound of formula (VI):

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(VI)

wherein X represents halogen.

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CLAIMS for the designated states: AT, ES, GR

1. A process for the preparation of an
oxadiazole compound, substituted on one of the ring
carbon atoms thereof with a non-aromatic azacyclic or
azabicyclic ring system; and substituted on the
other ring carbon with a substituent of low
lipophilicity, or a salt thereof; which process
comprises:

10

a) reacting a reactive derivative of a
carboxylic acid of formula R^aCO_2H , with either a
compound of formula (IIIA) or (IIIB) or a salt
thereof:

15



20

(IIIA)

(IIIB)

25 wherein one of R^a and R^b is a non-aromatic azacyclic
or azabicyclic ring system, and the other is a group
of low lipophilicity; or

b) reacting a compound of formula (IV):
 $R^a-CO-N=C(R^b)N(CH_3)_2$, with hydroxylamine; or

30

c) oxidizing an oxadiazoline with an
oxidizing agent; or

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d) when the non-lipophilic substituent is amino, reacting a compound of formula (IIIA) with a cyanogen halide; or

e) when the non-lipophilic substituent is
5 (C₁₋₃) alkoxycarbonyl, reacting a compound of formula:



15 with nitrous acid; or

f) when the desired product is a 1,3,4-oxadiazole, reacting a compound of formula R^a.CO.NH.NH.CO.R^b, with a dehydrating agent, at an elevated temperature.

20

2. A process as claimed in Claim 1 for the preparation of a compound having the formula (II):



or a pharmaceutically acceptable salt thereof;
wherein R¹ represents a non-aromatic azacyclic or
30 azabicyclic ring system; and R² represents a
substituent of low lipophilicity.

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3. A process as claimed in either Claim 1 or Claim 2 wherein the azabicyclic ring system is a pyrrolidine, quinuclidine or 1-azabicyclo[2,2,1]heptane ring, optionally substituted with methyl or hydroxy.

4. A process as claimed in any one of Claims 1 to 3 wherein the substituent of low lipophilicity is hydrogen, methyl, amino, methoxycarbonyl or ethoxycarbonyl.

5. A process as claimed in Claim 2 wherein R^2 represents amino.

6. A process as claimed in Claim 1 for the preparation of a compound which is:
3-[5-(3-amino-1,2,4-oxadiazol)-yl]quinuclidine;
5-[5-(3-amino-1,2,4-oxadiazol)-yl]quinuclidin-3-ol;
1-methyl-3-[5-(3-amino-1,2,4-oxadiazol)-yl]pyrrolidine;
3-[5-(3-amino-1,2,4-oxadiazol)-yl]-1-azabicyclo[2,2,1]heptane.

7. A process for the preparation of a pharmaceutical composition which comprises mixing a pharmaceutically acceptable carrier with a compound prepared as claimed in any one of Claims 1 to 6.

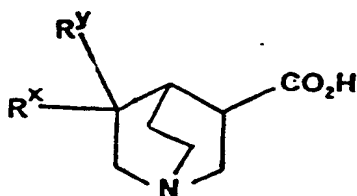
8. A process as claimed in Claim 7 which further comprises incorporating a peripheral cholinergic antagonist in the composition.

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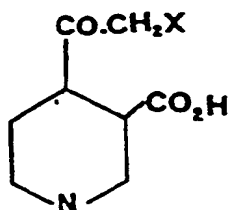
9. An intermediate of formula (V):



(V)

or a reactive derivative thereof, wherein R^X represents H and R^Y represents hydroxy, or R^X and R^Y together represent oxygen.

10. A process for the preparation of a compound as claimed in Claim 9 which comprises cyclisation of a compound of formula (VI):



(VI)

wherein X represents halogen.



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54 **Oxadiazoles useful in the treatment of senile dementia.**

57 A class of novel oxadiazoles, substituted on one of the ring carbon atoms with a non-aromatic azacyclic or azabicyclic ring, and substituted on the other ring carbon atom with a substituent of low lipophilicity; are potent muscarinic agonists, and have good CNS penetrability. The compounds are therefore useful in the treatment of neurological and mental illnesses.

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European Patent
Office

EUROPEAN SEARCH REPORT

0239309

Application number

EP 87 30 2296

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
A	FR-M- 4 840 (K. THOMAE) * Whole document *	1,7	C 07 D 453/02 C 07 D 413/04 C 07 D 451/02
A	EP-A-0 177 965 (SUMITOMO PHARMACEUTICALS) * Pages 74-89; claims *	1,7	C 07 D 487/04 C 07 D 471/08 C 07 D 221/22 C 07 D 209/52 A 61 K 31/41// (C 07 D 487/04 209:00 209:00) (C 07 D 471/07 221:00 221:00)
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			C 07 D 451/00 C 07 D 453/00 C 07 D 487/00 C 07 D 471/00 C 07 D 413/00 C 07 D 271/00
The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of the search 22-08-1988	Examiner ALLARD
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claims:
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

X LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions,

namely:

1. Claims 1-11: Oxadiazoles, their use and preparation
2. Claims 12,13: Quinuclidien derivatives not containing the essential part of the final products

- ☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
- ☐ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

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